Ministry of Higher Education
and Scientific Research
University of Diyala
College of Science
Department of Chemistry

Synthesis and Characterization of New Organic Compounds Derived from 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde and Evaluation their Biological Activity

A Thesis Submitted to the
Council of College of Science, University of Diyala
In Partial Fulfillment of the Requirements for the Degree
of Master of science in Chemistry
by

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B.Sc. Chemistry Science/ University of Tikrit 2015

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Dedication

To my beloved family for always supporting, encouraging, and standing by me I dedicate this thesis.

I also dedicate this thesis work to my soul mate my husband for helping me throughout this work in every details and his support was very special.

To our little princess (**Janna**) I dedicate my thesis work, who made our life more joyful and bright.

I dedicate this work and give special thanks to my husband's family for their support and love during the period of my project.

Acknowledgment

First and foremost I am thankful to the god Almighty my creator, my strong pillar, my source of inspiration, wisdom, knowledge and understanding. I am totally sure that this work would have never become truth, without His guidance.

I would like to express my wholehearted thanks to my family for their generous support they provided me throughout my entire life and particularly through this project. Because of their unconditional love and prayers, I have the chance to complete this thesis.

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Special thanks are due to my husband, I don't know where I would be now if it wasn't for you huge help in editing my many mistakes. You are truly an outstanding person and an able educator, I thank you from the bottom of my heart.

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Abstract

In the present research, new indole Schiff bases were synthesized from one of indole derivatives. The indole Schiff base derivatives are :

1- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(o-tolylimino) propanal

2- 3-((4-bromophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal

3- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal

4- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,4-dimethylphenyl)imino)propanal

5- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(p-tolylimino)propanal

6- 3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal

7- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal

8- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2-hydroxyphenyl)imino)propanal

9- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((3-hydroxyphenyl)imino)propanal

The chemic al structures of all new compounds have been characterized and confirmed by spectroscopic techniques such as, (FT-IR, ^{1}H-NMR, and APT ^{13}C-NMR), their purities tested by thin layer chromatography (TLC). Six new synthesized compounds evaluated for their cytotoxicity activity against AMJ-13 cell line of breast cancer and revealed a good results compare to the control.

The indolic aldehyde (2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde) was synthesized by Vilsmier-Haack reaction through the reaction of 1,1,2-trimethyl-1H-benzo[e]indole with Phosphoryl chloride ($POCl_3$) in the present of dimethyl formamide (DMF) as asolvent as shown below.

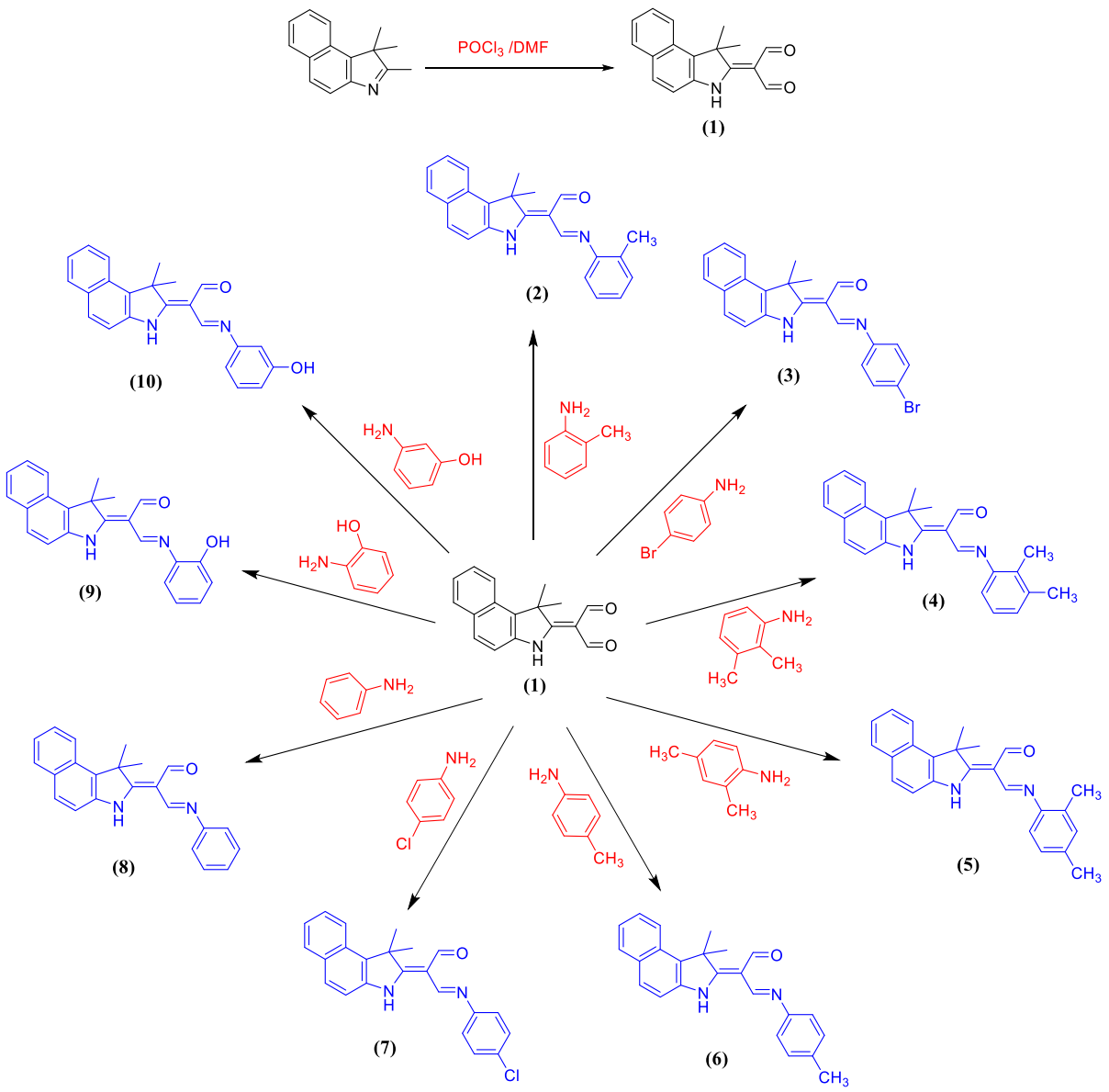
1,1,2-trimethyl-1*H*-benzo[*e*]indole

(1)

2-(1,1-dimethyl-1,3-dihydro-2*H*-benzo[*e*]indol-2-ylidene)malonaldehyde

The synthesized indolic aldehyde was considered as a precursor to synthesis various kinds of imines by reacting with different substituted anilines as shown in the scheme below

The cytotoxicity of the six synthesized derivatives were screened against AMJ-13 breast cancer cell line with three different concentrations 25, 50 and 100 µg/ml. studying the effect of the tested compounds in inhibitory of the AMJ-13 cell line with 48 h exposure time. Most of the tested derivatives exhibited acceptable inhibition rates against used cell line, compound (8) with 100 µg/ml concentration showed highest cytotoxicity with inhibition rate 67.9 % among rest of the tested compounds with variety of concentrations.



The general scheme of the synthesized compounds

Content

Content

List of Figures

Content

Content

Content

List of Schemes

List of Tables

Content

List of Abbreviations

$^{\circ}$C	Degree Celsius
LSD	Lysergic acid diethylamid
eπ	Ione pair of orpital P electrons
EAS	Electrophilic Aromatic Substitution
DFT	Discrete Fourier Transform
Kcal.mol	Kilo calories.Mole
Cp	cyclopentadienyl
Pym	pyrimidine
A	*Alfa*
B	*Beta*
DMF	Dimethyle formamide
CNS	Central nervous system
TLC	Thin Layer Chromatography
FTIR	Fourier-Transform Infrared
^{1}HNMR	Proton Nuclear Magnetic Resonance Spectrometer
^{13}CNMR	Carbon Nuclear Magnetic Resonance Spectrometer
APT ^{13}C NMR	Attached Proton Test ^{13}C- Nuclear Magnetic Resonance Spectrometer
Ml	Milliliters
mmol	Millimole
h, hrs	Hour, Hours
%	Percent
G	Gram
m.p.	Melting point
Cm	Centimeter
MHz	Megahertz
DMSO	Dimethyl Sulfoxide
Δ	Chemical shift
ppm	Part per million
S	Singlet
D	Doublet
T	Triplet
M	Multiplet
TMS	Tetramethylsilane
Ar	Aromatic ring
Rf	Retetion factor
ICCMGR	Iraqi Center for Cancer and Medical Genetics Research
HEPES	4(2-hydroxy ethyle)-1-piperazine ethanole sulfonic acid

CHAPTER ONE

INTRODUCTION

1. 1. Heterocyclic Compounds

Heterocyclic compounds probably constitute the most varied and largest family of organic compounds. Every carbocyclic compound (homocyclic compound), despite of structure and functionality, may in principle be changed over into a collection of heterocyclic analogs by replacing one of the ring carbon atom or more with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulfur (the most well-known heterocyclic elements), the permutations and combinations of such a replacement are various.[1] Heterocyclic compounds can be aromatic in nature as indicated by their chemical structure such as pyrrole, furan and thiophene figure (1. 1). Or aliphatic like pyrrolidine and tetrahydrofuran, figure (1. 2).

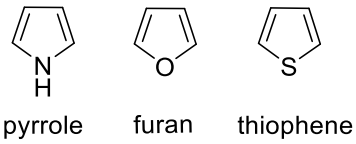


figure (1. 1): The chemical structure of pyrrole furan, and thiophene

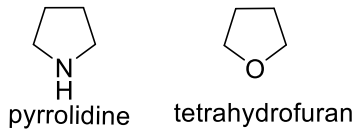


figure (1. 2): The chemical structure of pyrrolidine and tetrahydrofuran

The aromatic heterocyclic rings can be five-membered. They may include one heteroatom such as pyrrole, furan, and thiophene, or two heteroatom as in oxazole ring which comprises of one oxygen atom and one nitrogen atom, or in thiozole which contains

one nitrogen atom and one sulfur atom, and in imidazole ring which comprises of two nitrogen atoms figure (1. 3).

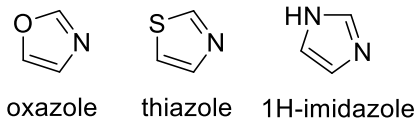


figure (1. 3): The chemical structure of oxazole, thiozole and 1*H*-imidazole

These heterocyclic rings could be fused with benzene ring to give compounds like indole, benzofuran, and benzothiophene.[2] figure (1. 4).

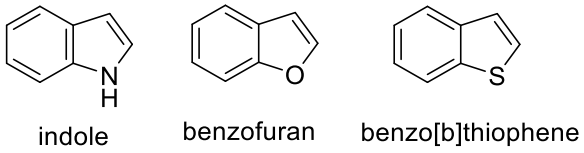


figure (1. 4): The chemical structure of indole, benzofuran, and benzothiophene

Most of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers utilized in industrial applications running from cosmetics, reprography, information storage and plastics are heterocyclic in nature.[3] One striking structural feature inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three-dimensional representations. Between them, nitrogen and sulfur -containing heterocyclic compounds have kept up the interest of researchers through decades of historical development of organic synthesis.[4]

1.2. Indole

Indole is a bicyclic aromatic heterocyclic organic compound[5] Consisting of a six membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring figure (1. 5). In 1866, Baeyer and knop,[6] in the course of a study of the structure of indigo, reduced isatin and obtained two products, C_8H_7NO and $C_8H_7NO_2$ (oxindole and dioxindole), which they considered as hydroxyl derivatives of C_8H_7N; they named the latter indole. The work was proceeded by Baeyer and Emmerling, proposed in 1869 the formula which is generally accepted.[7-9]

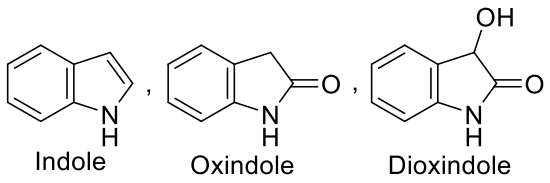


figure (1. 5): The chemical structure of indole, oxindole, and dioxindole

Indole derivatives occur widespread in many natural products has been produced, usually in small amount, by extraction from naturally occurring materials by methods which recommend that the indole so obtained is in many cases the result of breakdown of its derivatives. Different plants have yielded indole, among them the following: Robinia pseudacacia,[10] the jasmines,[11,12] certain citrus plants, and orange blossoms. [13] Indole is also found after putrefactive processes have occured. It's found in the animal body wherever pus formation occurs and in the pancreas, and liver, the bile, and brain. It's formed in the putrefaction of milk, of blood fibrin, of albumin, and possibly of vegetable protein. Formation of indole is probably the result of the decomposition of tryptophan in these cases of putrefaction of protein material. Indole has also been

found to be present in coal tar in the fraction boiling between 240° 260° C. [14,15]

The discovery of indomethacin [16] figure (1. 6) as a successful agent for clinical treatment of anti-inflammatory disorders has led to the investigation of indole moiety to obtain better anti-inflammatory agents.

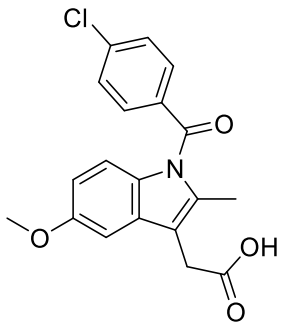


figure (1. 6): The chemical structure of Indomethacin

Furthermore indole and its analogs possess wide range of biological activities, such as anti-inflammatory [17-20], anti-microbial [21,22], anti-bacterial [23,24], anticonvulsant [25,26] and cardiovascular activity. [27]

The Indole is an important heterocyclic system because it provides the skeleton of indole alkaloids—biologically active compounds from plants including strychnine figure 1. 7 and Lysergic acid diethylamide (LSD) (figure 1. 8), because it is the basis of drugs like indomethacin, and because it is built into proteins in the form of amino acid tryptophan.[28]

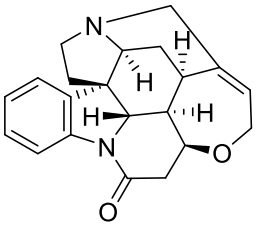


Figure (1. 7): The chemical structure of strychnine

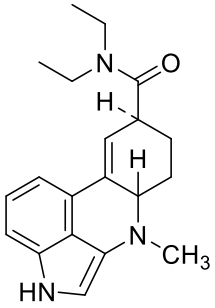


figure (1. 8): The chemical structure of Lysergic acid diethylamide (LSD)

1. 2. 1. Properties of Indole

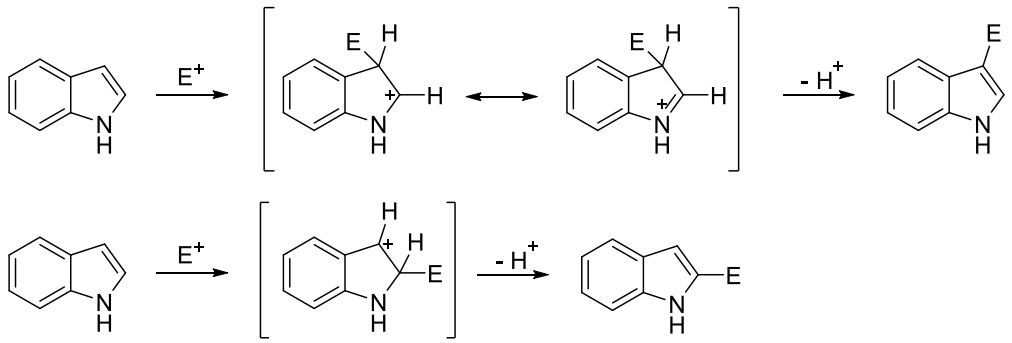
Indole is a colorless crystalline solid in the form of shinning leaflets. It is volatile with steam. indole melts at 52°C and boils at 253°C. It is soluble in hot water and in hot alcohol, and it is also soluble in benzene and in ether. The compound in the impure state has unpleasant odor.(29)

The indole nucleus is a planar bicyclic molecule containing 10π electrons (8π electrons from double bonds and 2π electrons from lone pair of electrons from nitrogen), thus it is aromatic according to Huckel's rule. It acts as a weak base and protonates only in the presence of strong acids.(30)

1. 2. 2. General Reactivity of Indole

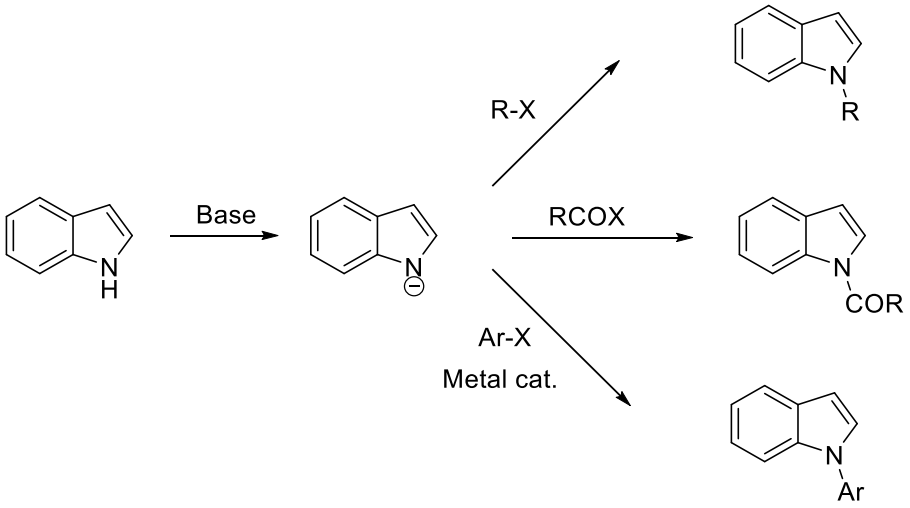
Indole is a π-excessive aromatic heterocycle with ten π-electrons. The lone pair of the nitrogen atom (which features sp2 hybridization) completes the ten π-electrons delocalized across the

ring. As in pyrrole, the π-excessive nature of the aromatic ring detects its reactivity and chemical properties. Indole is a weak base (pKa -2,4 for the conjugated acid), as protonation of the nitrogen atom would deactivate the aromaticity of the five-membered ring. In contrast, as a π-excessive aromatic heterocycle, electrophilic aromatic substitution (EAS) is one of the most characteristic reactions. Unlike pyrrole, addition of electrophiles occures preferentially at C3.[31] Indole shows up high EAS reactivity, which is estimated to be orders of magnitude greater than benzene. This is due to electron-rich nature of indole, and the high electron density at its 3-position is responsible for indole's regioselectivity toward EAS reactions [32] scheme (1. 1)



scheme (1. 1): Possible regioisomers in the electrophilic attack on the indole ring

The indole N-H is weakly acidic, so can be deprotonated by strong bases (pka 16.7 in water) to provide the indolyl anion. Therefore, substitution at the nitrogen can be done through base-promoted processes, such as acylations, alkylations, and, more recently transition metal catalyzed arylations[31,33] scheme (1. 2).



Scheme (1. 2): Deprotonation of indole by strong base

1. 2. 3. Tautomers and Isomers of Indole

The 2H-indole and 3H-indole are tautomers of 1H-indole figure(1. 9). Both systems are highly unstable, although 3H-indole has been characterized spectroscopically, and its derivatives have been isolated.[34] High level quantum chemical Discrete Fourier Transform (DFT) calculations predict an energy difference of 5.20 and 24.10 Kcal.mol^{-1} between 1H-indole and 3H-indole, and 1H-indole and 2H-indole respectively. The other isomeric benzopyroles are isoindole and indolizine. [31] figure (1. 9).

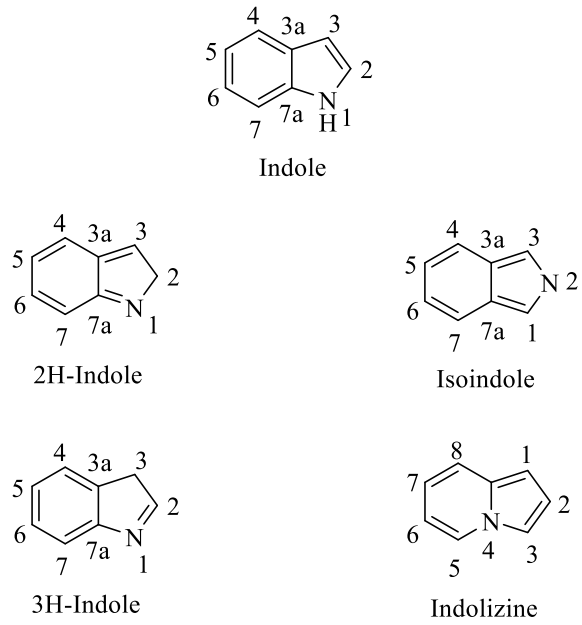
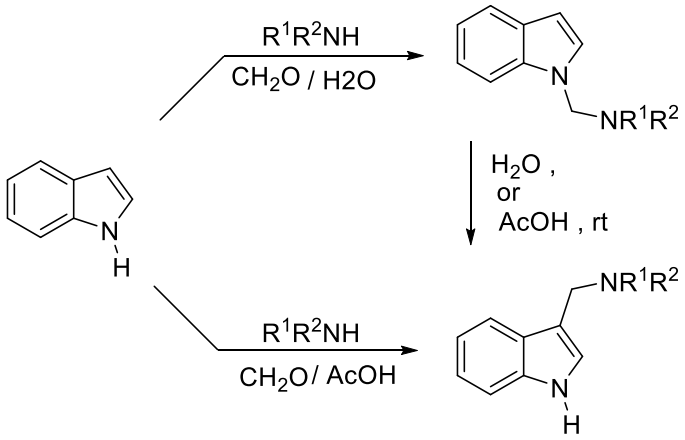


figure (1. 9): Indole, tautomers and isomers with conventional numbering

1.2.4. Reactions of Indole

1.2.4.1. Mannich Reaction

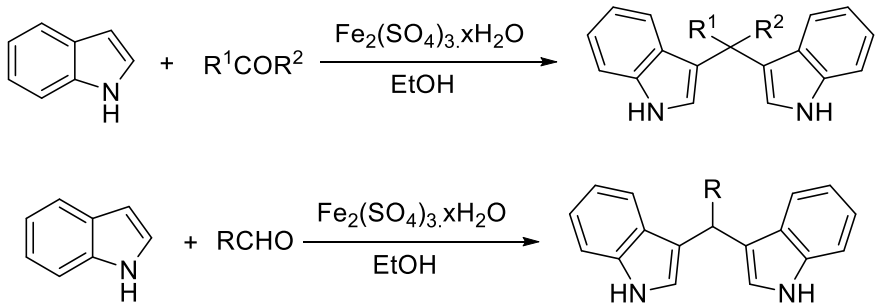
Under typical Mannich's conditions, indole undergoes alkylation at C3. This reaction leads to the synthesis of gramines which are significant intermediates for the preparation of substituted indoles. When the reactions are conducted in water at low temperatures, the kinetically controlled N-alkylation product is produced , the resulting N-aminal indoles are relatively stable but convert into the thermodynamically more stable C3-substituted aminomethyl indoles via heating at neutral pH or acid treatment at room temperature[35] scheme (1. 3).



scheme (1. 3): Mannich's Reaction of Indole

1. 2. 4. 2. Reactions of indole with aldehydes, ketones in the presence of (a) Hydrated ferric-sulfate, (b) Silica gel.

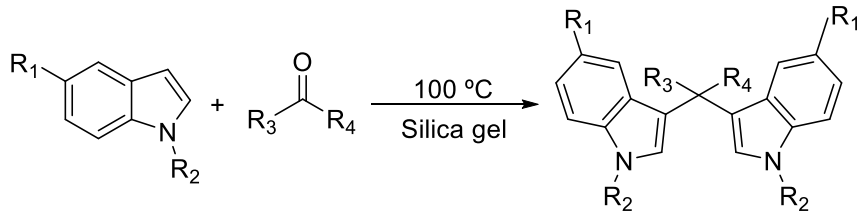
Hydrated ferric sulfate [$Fe_2(SO_4)_3.xH_2O$] has been found to be an Effective catalyst for condensation of bisindoles with aliphatic or aryl aldehydes and ketones including methyl and ethyl-alkyl ketones, methyl aryl ketones, cyclic ketones. [36]



scheme (1. 4): Reactions of indole with aldehydes, ketones in the presence of hydrated ferric-sulfate

A simple, clean, and effective solvent-free protocol were described for the synthesis of bis(indolyl)methanes promoted by silica gel. The products were gained in good to excellent yields through the reaction of indoles with cyclohexanone and a range of

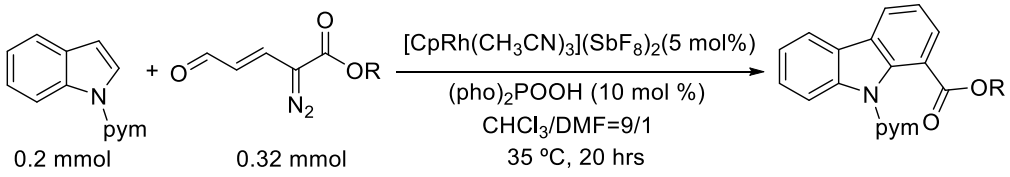
aldehydes. The silica gel was easily recovered and used for further reactions without activity lossing . [37]



scheme (1. 5): Reactions of indole with aldehydes, ketones in the presence of silica gel

1. 2. 4. 3. Reaction of Indoles with Enaldiazo Esters in the presence of tandem catalyst.

A tandem CpRh(III)-catalyzed C−H activation/Bronsted acid-catalyzed intramolecular cyclization lets a facile synthesis of carbazoles from easily obtainable indoles. The reaction proceeds under rather mild reaction conditions with the generation of water and N_2 as the only byproducts. Broad substrate field, excellent functional group tolerance, and high yields were obtained. [38]

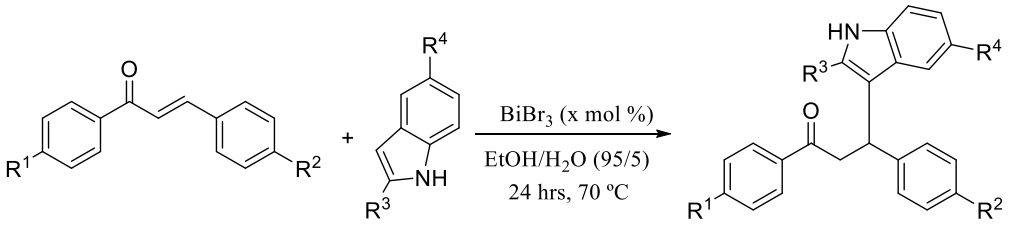


scheme (1. 6): Reactions of indole with Enaldiazo Esters in the presence of tandem catalyst.

1. 2. 4. 4. Conjugate Addition of Indoles to α,β-Unsaturated Ketones by Using Bismuth (III) Bromide.

An effective method for the conjugate addition of indoles to a Different of chalcones using $BiBr_3$ in ethanol is reported. Products are isolated by a simple method that avoids an aqueous

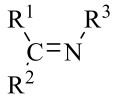
work up and extensive chromatography, thus decreasing waste. Bismuth (III) compounds are especially attractive from a green chemistry perspective because they are remarkably nontoxic, non-corrosive and relatively inexpensive. (39)



scheme (1. 7): Reactions of indole with Conjugate α,β-Unsaturated Ketones by Using Bismuth (III) Bromide.

1. 3. Schiff bases

Schiff bases, named after Hugo Schiff ,(40) are produced when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known as azomethine or imine) figure (1. 10) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C=O) has been exchanged by an azomethine or imine group. (41)



R^1, R^2 and/or R^3=alkyl, aryl or H

Figure (1. 10): General structure of a Schiff base

Schiff bases are some of the most broadly used organic compounds. They are used as dyes and pigments, catalysts, intermediates in organic synthesis, and as polymer stabilisers (42) , Schiff bases have also been shown to exhibit a wide range of biological activities, including antibacterial, antifungal, anti-

inflammatory, antimalarial, antiviral, antiproliferative, and antipyretic properties. [42-44]

Azomethine or imine groups are exsist in various natural, natural-derivatives, and non-natural compounds. The azomethine group present in such compounds has been shown to be critical to their biological activities. [45-47] (figure 1. 11)

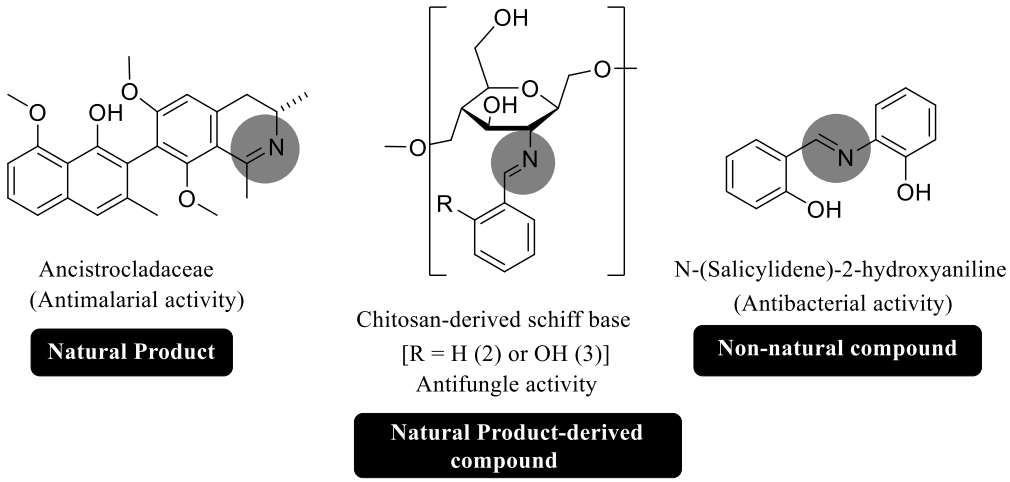
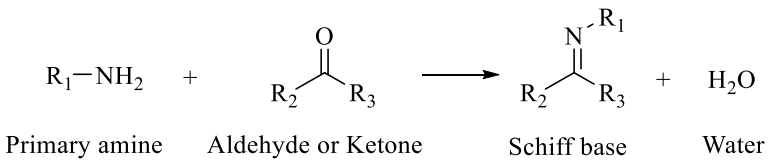


figure (1. 11): Example of bioactive Schiff bases

1. 3. 1. Synthesis of schiff bases

The first preparation of schiff base was achieved in the 19th century by Schiff (1864). Since then a Different of methods for the synthesis of schiff bases have been described,[48] A Schiff base reaction is a reversible, acid-catalysed condensation between a primary amine (not ammonia) and an aldehyde or ketone, which is shown in scheme (1. 8) where R may be an alkyl or an aryl group.

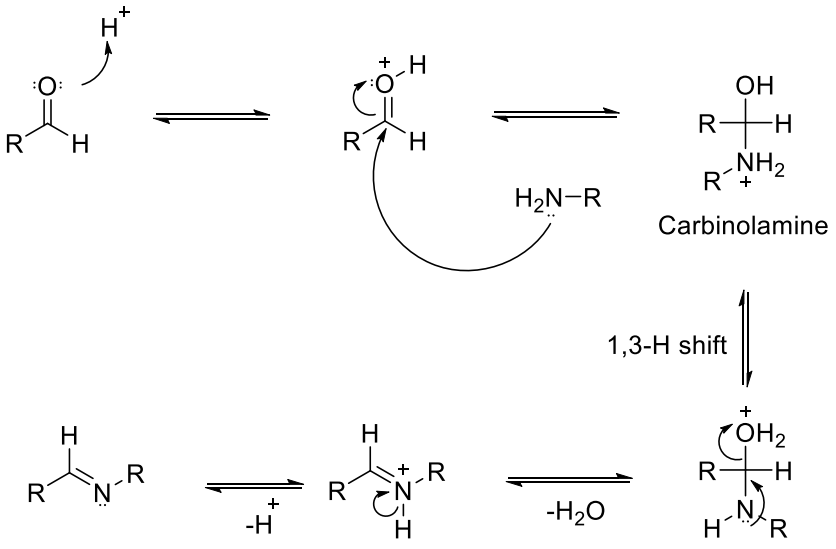


scheme (1. 8): Preparation of Schiff base

Usually, the formation of Schiff bases from aldehydes or ketones requires a protic solvent which is sufficiently dry in order to avoid potential hydrolysis of the newly formed imine bond. The formation is generally undertaken under acid or base catalysis, or via heating. The completion of imine formation is controlled by the separation of the product or removal of water, or both. [49]

1. 3. 2. Mechanism of Schiff bases formation

The general concept of the mechanism of Schiff base formation, as shown in scheme (1. 9) is nucleophilic addition to the carbonyl group. During Schiff base formation, the primary amine is the nucleophile. In the first part of the mechanism, the lone pair of electrons in the amine nitrogen attacks the aldehyde or ketone to give an unstable addition compound called a (carbinolamine).[50] Then a 1,3-hydrogen shift follows which simplify losing water by either acid or base catalysis. Since the carbinolamine is an alcohol, it undergoes acid catalysed dehydration.

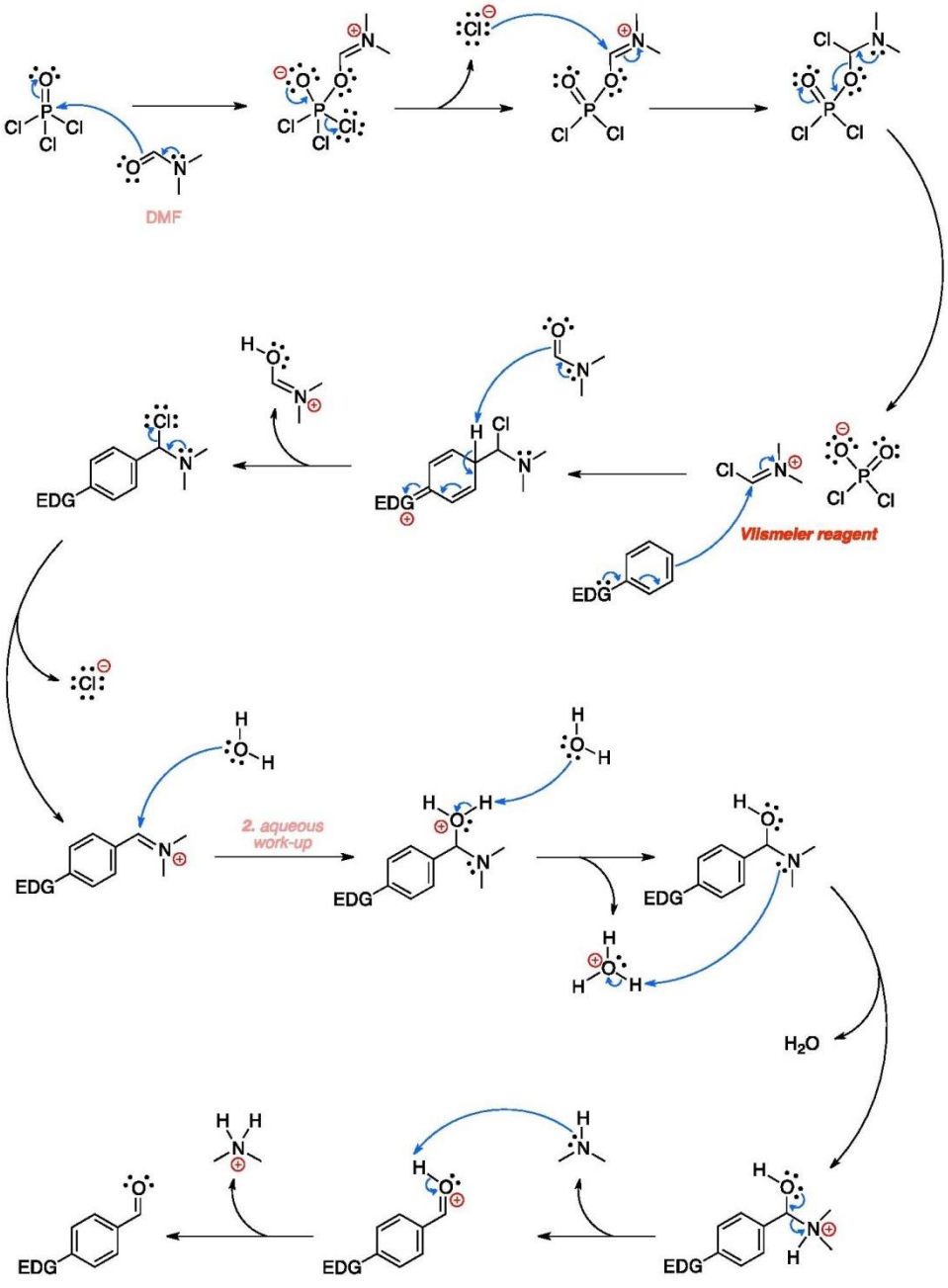


scheme (1. 9): Mechanism of Schiff base formation

1. 4. Vilsmeier – Haack Reaction

The Vilsmeier-Haack reagent is an effective, economical and mild reagent for the formylation of reactive aromatic and heteroaromatic substrates[51]. in the precent time used as a powerful synthetic tool for the construction of many heterocyclic compounds.[52-54] The classical Vilsmeier-Haack reaction[55], however, includes electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt to get the corresponding iminium species, which facilitates easy entry into different nitrogen and oxygen based heterocycles. [56]

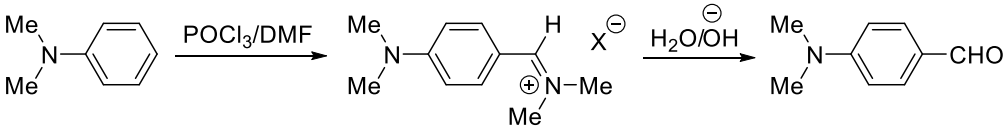
The reaction of an N,N-disubstituted formamide, like di methylformamide (DMF) or N-methylformanilide, with acid chlorides, such as phosphoryl chloride or phosgene, leads to the formation of adducts. These adducts which are usually referred to as the Vilsmeier-Haack reagent find important applications in synthetic organic chemistry specially in the formylation of electron rich aromatic compounds or alkenes. In the present time it is well established that the reaction proceeds by the attack of the carbonyl oxygen of the amide to form the adduct at first which reacts further to give chloromethylene iminium salt scheme (1. 10). [57]



Scheme (1. 10): Vilsmeier Haack mechanism

The classical vilsmieir-Haack reaction involves the reaction of electron rich aromatic compounds or alkenes with the iminium salts produced from formamides and acid chlorides.

The vilsmieir-Haack reaction is an important method for the synthesis of sevsral aromatic aldehydes and α,β-unsaturated aldehydes Scheme (1. 11). [58]



Scheme (1. 11): Vilsmieir-Haack reaction for the synthesis of aromatic aldehydes

1. 5. Biological activity of indole Schiff bases

The indole ring system is probably t Widespread heterocycle in nature. Owing to the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an significant structural component in many natural products with high structural complexities and biologically active molecules. For this reason, indole and its derivatives have been utilized, continuously, in different research areas such as fragrances, pharmaceuticals, pigments, agrochemicals, and material science. [59] Schiff bases are important type of compounds in pharmaceutical and medicinal field. They exhibit biological applications including antibacterial [60-64], antifungal [61-64] and antitumor activity [65,66]. Identically indole derivatives are prepared for a long time for a variety of biological activities such as treatment of CNS, anticancerous, antidepressant, antihistaminic, antibiotic, anticonvulsants and many others. Electron-rich nitrogen

heterocyclic compounds play an important role in varied biological activities. (67)

Fadhil L. Faraj *et al* synthesized 2-(5-Chloro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-3-(2,4-disubstituted phenylimino)-propionaldehyde and were evaluated for their in vitro against– AMJ breast cancer cell line. The appeared data showed that compounds have promising anticancer activity toward AMJ13 cell line at low concentrations figure (1. 12). (68)

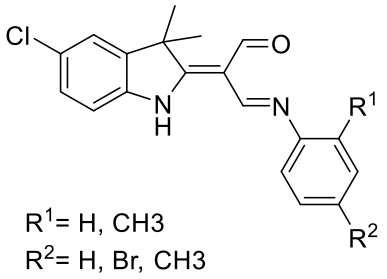


figure (1. 12): 2-(5-Chloro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-3-(2,4-disubstituted phenylimino)-propionaldehyde

Anand R. Saundane *et al* synthesized N'-[(5-substituted-2-phenyl-1H-indol-3-yl)methylene] 2-oxo-2H-chromene-3-carbohydrazides and were screened for their antimicrobial and antioxidant activities. The synthesized derivatives showed acceptable activities as antimicrobial and antioxidant agents figure (1. 13). (69)

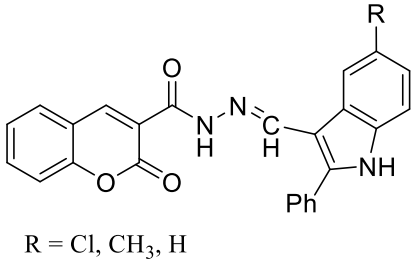


figure (1. 13): N'-[(5-substituted-2- phenyl-1H-indol-3-yl)methylene] 2-oxo-2H-chromene-3-carbohydrazides

Syahrul Imran *et al* synthesized bisindolylmethane Schiff base derivatives and evaluated them for their antibacterial activity against selected Gram-positive and Gram-negative bacterial strains (*Salmonella typhi*, *S. paratyphi* A and *S. paratyphi* B). The synthesized derivatives showed moderate to good antibacterial activity against bacteria strains used. (70)

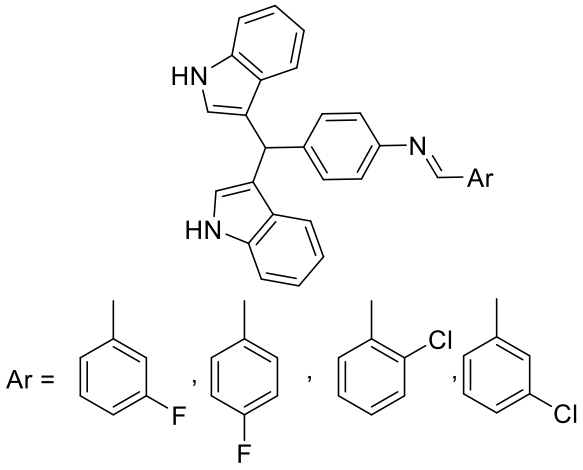


figure (1. 14): (E)-N-(4-(di(1H-indol-3-yl)methyl)phenyl)-1-(substituted phenyl)methanimine

Gokce Gurkok *et al* synthesized new series of (E)-3-((2-(substituted phenyl)hydrazono)methyl)-1H-indole derivatives, and were evaluated for their antimicrobial activity. Tested compounds displayed significant activity against used microorganisms. (71)

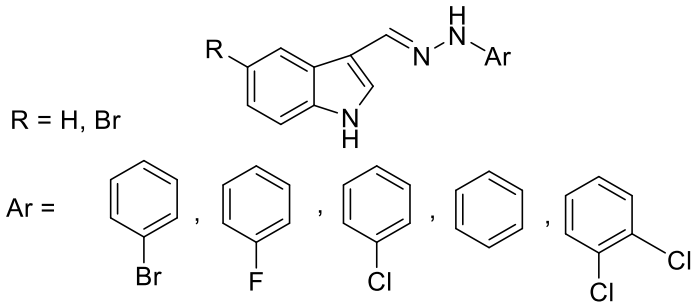


figure (1. 15): (E)-N-(4-(di(1H-indol-3-yl)methyl)phenyl)-1-(substituted phenyl)methanimine

1. 5. 1. Cancer

Cancer considered to be one of the major reasons of deaths in the 20st century and increasing occurrence in 21st century. This represents main world health problem. Almost 7.6 million deaths are usually caused by cancer which represents (13%) of all deaths.(72) The cancer represents abnormal cell growth which means that some of the cells start to divide without stopping chance by ignoring the usual rules of normal cell division and these cells begin to invade to the surrounding tissues and this is called as "metastasis". (73)

There are several causes of cancer: family history, age, bacterial infection, viral infection, smoking, contact to radiation and chemicals, alcohol use and drinking, eating, touching or breathing harmful materials, these cancer causing are called "carcinogens" and contact to these carcinogen does not mean you will get cancer but depends on how many times you are exposed to it. (74)

There are many types of cancer such as breast, blood, prostate, lung, brain and colon cancer which is considered the most common cancer types appears in Iraq.(75)

Breast cancer was considered one of the most common diagnosed type in the women around the world. (76) In each year about 600,000 women around the world were death because of it. (77) American Cancer Society's estimated that breast cancer is the most common type in American women. In 2017 About 252,710 new cases of breast cancer in women were diagnosed and about 40,610 were died from it. (78) Also the percentage deaths of cancer in Asian women has increased more rapid rate in every year.(79)

Aim of the work

The main objectives of the present study are :

1- Synthesis new derivatives of indole based Schiff bases.

2- Characterization the chemical structure of the synthesized compounds by spectral techniques (FT-IR, ^{1}H, APT ^{13}C NMR).

3- Evaluating anticancer activity of the synthesized derivatives against AMJ-13 breast cancer cell line.

CHAPTER TWO

EXPERIMENTAL PART

2.1. Chemistry part

2. 1. 1. Materials

All starting materials and solvents used in this project were purchased from different companies, as listed in the table (2. 1). These materials used as received without additional purification. 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)

malonaldehyde was synthesized according to the procedure mentioned by [80] the completion of the reaction was checked by using thin layer chromatography TLC (mobile phase Ethyl acetate:Hexane 1:3).

Table (2. 1): Chemicals and solvents used in the chemistry part

No.	Chemicals	Purity	Company
1	Aniline	99.5 %	Thomas Baker
2	4-bromo aniline	97 %	Merck
3	4-chloro aniline	98 %	BDH
4	2,3-dimethyl aniline	99 %	Merck
5	2,4-dimethyl aniline	99.5 %	Merck
6	Dimethyl formamide	99.9 %	Romil
7	Ethanol	99 %	Scharlau
8	Ethyl acetate	99 %	Romil
9	Glacial acetic acid	99.9 %	Chemlab NV
10	n-Hexane	99 %	Sigma Aldrich
11	2-Hydroxy aniline	98 %	Merck
12	3-Hydroxy aniline	98 %	Merck
13	2-methyl aniline	99 %	Merck
14	Phosphoryl chloride	99.5 %	Merck
15	Sodium hydroxide	98 %	Thomas Baker
16	1,1,2-trimethyl-1H-benzo[e]indole	98 %	Sigma Aldrich

2. 1. 2. Instruments

- Fourier-transform infrared spectroscopy (FTIR): IR spectra recorded on a Perkin-Elmer Spectrum version 10.02 by using KBr disk in the Department of Chemistry, College of Science, University of Diyala.

- Nuclear Magnetic Resonance Spectrometer (NMR): ^{1}H NMR, ^{13}C NMR and APT ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in University of Science and Technology, College of Science, Irbid City, Jordan .

- Thin Layer Chromatography (TLC): Thin layer chromatography (TLC) was performed by using alumina plates (size 20×20 cm) percolated with silica gel. the spots were detected by using fluorescence analysis cabinet model CM-10. In the the Department of Chemistry, College of Science, University of Diyala.

- Melting Point: The melting points of the synthesized compounds were determined by using the stuart SMP[10] electronic apparatus, at the the Department of Chemistry, College of Science, University of Diyala.
- Rotary Evaporator: The solvents were evaporated by using Heldove apparatus, HeiVAP, Germany in the Department of Chemistry, College of Science, University of Diyala.

2. 1. 3. Synthetic methods

2. 1. 3. 1. Synthesis of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde (**1**) as demonstrated in figure (2. 1)

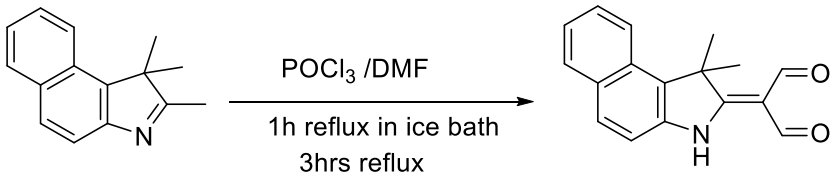
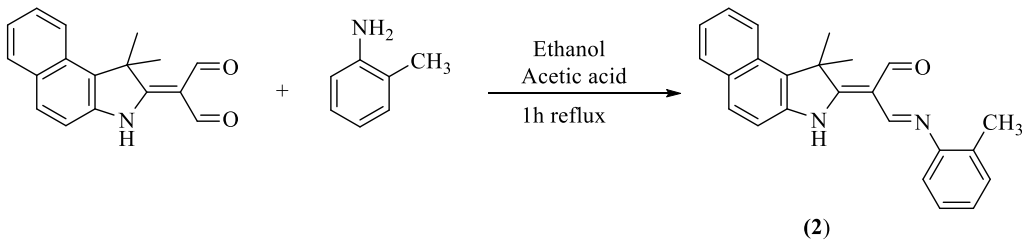


figure (2. 1): The synthetic pathway of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde **(1)**

N,*N*-dimethyl formamide (DMF) (3ml) was cooled in an ice bath then added drop wise of (1.3ml) Phosphoryl chloride ($POCl_3$) with stirring under 5°C, then a solution of (1 g, 4.7 mmol) 1,1,2-trimethyl-1H-benzo[e]indole in DMF (3ml) was added dropwise, the reaction mixture was stirred in ice path for 1h. then reflux for 3h. at 88 ºC. The resulting solution was added to icy distilled water and neutralized with 25% NaOH aqueous, the yellow precipitate was formed filtered off and dried in oven. Recrystyled by ethanol to afford pure yellow precipitate. [80] Yield: (1.243 g, 98%). m.p. 202-203 ºC.

2. 1. 3. 2. Synthesis of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(o-tolylimino)propanal (**2**) as elucidated in figure (2. 2)

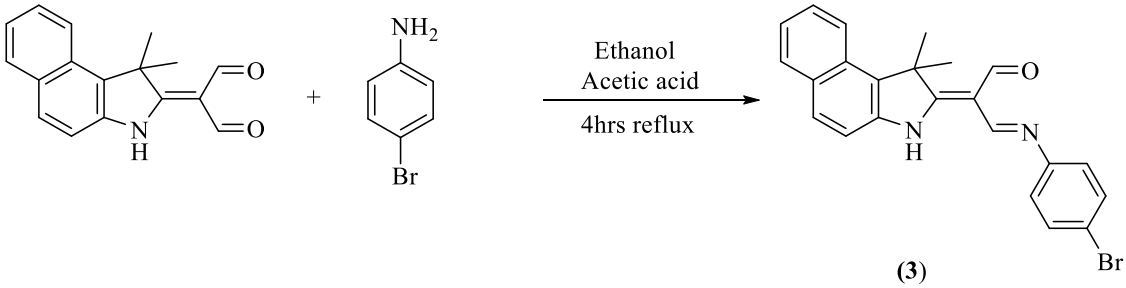


(**2**)

figure (2. 2): The synthetic pathway of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(o-tolylimino)propanal (2)

A solution of (0.3 g, 1.13 mmol) of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde **(1)** was dissolved in ethanol 15 ml and solution of (0.12 g, 1.13 mmol) of 2-methyl aniline was dissolved in ethanol 10ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 1h. A solvent was reduced to one quarter; yellow precipitate was formed direct, filtered off and recrystyled by ethanol to afford pure yellow precipitate and dried in oven. [81] The completion of the reaction was checked by using TLC (3:2) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.36 g, 90%), m.p. 281-282ºC. IR data in (cm^{-1}): 3453 υ(NH), 3054 υ(CH aromatic), 2965 and 2930 υ(CH aliphatic), 2866 and 2725 υ(CH aldehyde), 1666 υ(CH=O), 1624 υ(HC=N), 1598 υ(C=C), 1328 υ(C-H of CH_3), 1269 υ(C-N) and 749 υ(C-H bending). ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 14.59 (s, 1H, N*H*), 9.7 (s, 1H, C*H*O), 8.4 (s, 1H, C*H*=N), 8.11-7.22 (Ar-*H*), 2.2 (s, 3H, CH_3), 1.80 (s, 6H, 2xCH_3). ^{13}C NMR of (100 MHz, DMSO-d_6) δ (ppm): 186.57 (*C*HO)), 184.49(NH-*C*=C), 152.3 (CH=N), 147.5, 139.32, 137.97, 132.53, 130.03, 129.56, 129.27, 127.99, 125.34, 127.09, 124.77, 123.30, 120.25 and 114.71, (*Ar*-H), 107.84 (C=*C*-CHO, 55.03 (CH_3-*C*-CH_3), 21 (CH_3-Ar), and 17.87 (2x *C*H_3).

2. 1. 3. 3. Synthesis of 3-((4-bromophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal **(3)** as demonstrated in figure (2. 3)



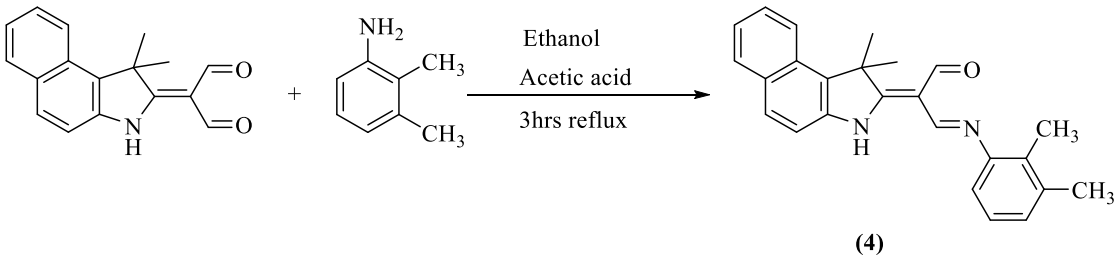
(**3**)

figure (2. 3): The synthetic pathway of 3-((4-bromophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal **(3)**

A solution of (0.5 g, 1.8 mmol) of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde **(1)** was dissolved in ethanol 25 ml and (0.33 g, 1.8 mmol) of 4-bromo aniline was dissolved in ethanol 15ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 4hrs. A solvent was reduced to one quarter; yellow precipitate was formed direct, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. [81] The completion of the reaction was checked by using TLC (3:2) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.672 g, 85%), m.p. 169-170ºC. IR data in (cm^{-1}): 3453 υ(NH), 3054 (CH aromatic) 2971 and 2930 υ(CH aliphatic), 2866 and 2683 υ(CH aldehyde), 1663υ (CH=O), 1619 υ(CHN), 1569 υ(C=C), 1325 υ(CH of CH_3), 1240 υ(C-N), 817 υ(C-Br) and 746 υ(C-H bending). ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 14.44 (s, 1H, N*H*), 9.75 (s, 1H, C*H*O), 8.33 (s, 1H, C*H*=N), 8.07-7.11 (Ar-*H*), 8.02-7.11 (Ar-*H*), 7.95 (d, 2H, Ar-*H*), 7.64 (m, 3H, Ar-*H*), 7.54 (d, 2H, Ar-*H*), 7.11 (t, 2H, Ar-H), 1.87 (s, 6H, 2xCH_3). ^{13}C NMR of (100 MHz, DMSO-d_6) δ (ppm): 187.05 (*C*HO)), 184.35(NH-*C*=C), 153 (CH=N), 146.93, 139.32, 137.97,

132.53, 130.03, 129.56, 129.27, 127.99, 125.34, 127.09, 124.77, 123.30, 120.25 and 118.01, (*Ar*-H), 108.07 (C=*C*-CHO, 55.30 (CH_3-*C*-CH_3) and 22.69 (2x *C*H_3).

2. 1. 3. 4. Synthesis of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal **(4)** as demonstrated in figure (2. 4)



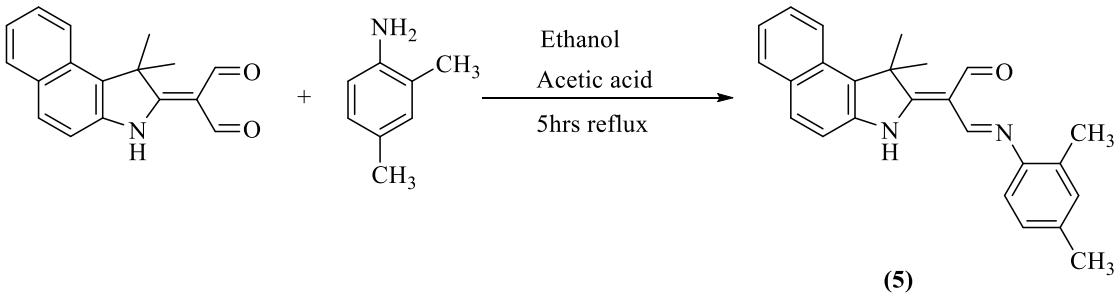
(4)

figure (2. 4): The synthetic pathway of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal **(4)**

A solution of (0.5 g, 1.8 mmol) of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde **(1)** was dissolved in ethanol 25 ml and (0.23 g, 1.8 mmol) of 2,3-dimethylaniline was dissolved in ethanol 10ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 3hrs. A solvent was reduced to one quarter; yellow precipitate was formed direct, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. [81] The completion of the reaction was checked by using TLC (3:2) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.56 g, 80%), m.p. 211-212ºC. IR data in (cm^{-1}) 3447υ (NH), 3053 υ(CH aromatic), 2963 and 2928 υ(CH aliphatic), 2866 and 2707 υ(CH aldehyde), 1662 υ(CH=O), 1617 υ(HC=N), 1579 υ(C=C), 1338 υ(CH of CH_3), 1272 υ(C-N) and 771 υ(C-H bending). ^{1}H NMR (400MHz, $CDCl_3$-d_6) δ (ppm): 14.55 (s, 1H, N*H*), 9.70 (s, 1H, C*H*O), 8.37 (s, 1H, C*H*=N), 8.08 (d, 1H, Ar-

H), 8.02-7.02 (Ar-*H*), 2.46 (s, 3H, CH_3), 2.35 (s, 3H, C*H*$_3$). ,1.89 (s, 6H, 2xC*H*$_3$).). ^{13}C NMR of (100 MHz, DMSO-d_6) δ (ppm): 187.36 (*C*HO)), 185.47(NH-*C*=C), 148.8 (CH=N), 138.94, 137.97, 132.53, 130.03, 129.56, 129.27, 127.99, 125.34, 127.09, 124.77, 123.30, 120.25 and 113.99, (*Ar*-H), 108.37 (C=*C*-CHO, 55.85 (CH_3-*C*-CH_3), 22.41 (CH_3-Ar), 20.75 (CH_3-Ar), and 14.09 (2x *C*H_3).

2. 1. 3. 5. Synthesis of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,4-dimethylphenyl)imino)propanal **(5)** as demonstrated in figure (2. 5)



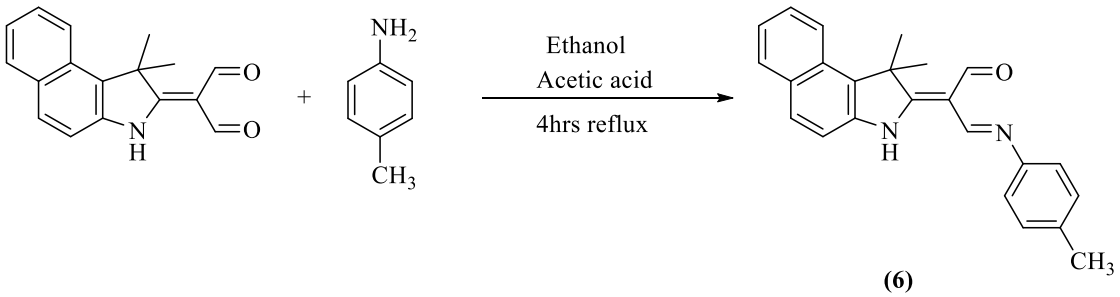
(5)

figure (2. 5): The synthetic pathway of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,4-dimethylphenyl)imino)propanal **(5)**

A solution of (0.5 g, 1.8 mmol) of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde **(1)** was dissolved in ethanol 25 ml and (0.23 g, 1.8 mmol) of 2,4-dimethylaniline was dissolved in ethanol 10ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 5h. A solvent was reduced to one quarter; yellow precipitate was formed direct, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. [81] The completion of the reaction was checked by using TLC (3:2) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.58 g, 83.5%), m.p. 152-153ºC. IR data in (cm^{-1}): 3454 υ(NH), 3046 υ(CH aromatic), 2984 and 2922 υ(CH

aliphatic), 2866 and 2721 υ(CH aldehyde),1669 υ(CH=O), 1624 υ(HC=N), 1579 υ(C=C), 1334 υ(CH_3), 1255 υ(C-N) and 743 υ(C-H bending). ^{1}H NMR (400MHz, $CDCl_3$-d_1) δ (ppm): 14.49 (s, 1H, N*H*), 9.70 (s, 1H, C*H*O), 8.35 (s, 1H, C*H*=N), 8.08-7.04 (Ar-*H*), 2.94 (s, H, CH_3), 2.3 (s, H, CH_3) ,1.91 (s, 6H, 2xCH_3). ^{13}C NMR of (100 MHz, DMSO-d_6) δ (ppm): 187 (*C*HO)), 185.27 (NH-*C*=C), 153 (CH=N), 148.35, 139.32, 137.97, 132.53, 130.03, 129.56, 129.27, 127.99, 125.34, 127.09, 124.77, 123.30, 120.25 and 115, (*Ar*-H), 107.99 (C=*C*-CHO, 55.63 (CH_3-*C*-CH_3), 22.16 (CH_3-Ar), 20.76(CH_3-Ar), and 18.06 (2x *C*H_3).

2. 1. 3. 6. Synthesis of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(p-tolylimino)propanal **(6)** as demonstrated in figure (2. 6)



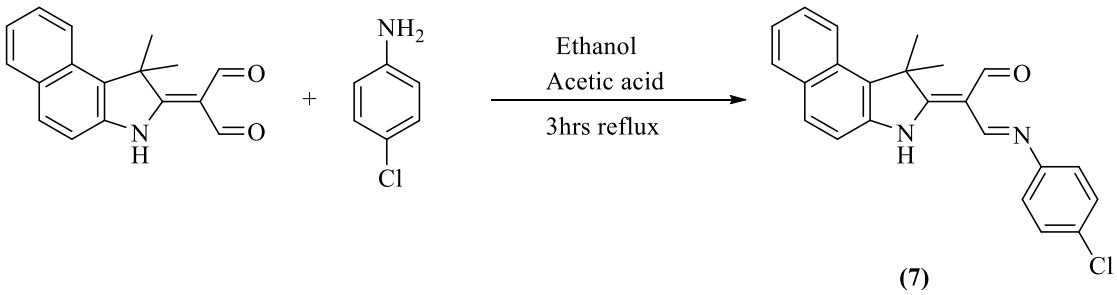
(6)

figure (2. 6): The synthetic pathway of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(p-tolylimino)propanal **(6)**

A solution of (0.5 g,1.8 mmol) of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde **(1)** was dissolved in ethanol 25 ml and (0.2 g,1.8 mmol) of 3-methyl anililne was dissolved in ethanol 10ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 4hrs. A solvent was reduced to one quarter; yellow precipitate was formed direct, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. [81] The completion of the reaction was checked by using

TLC (3:2) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.55 g, 82%), m.p. 141-142ºC. IR data in (cm^{-1}): 3025 υ(CH aromatic), 2970 and 2928 υ(CH aliphatic), 2866 and 2694 υ(CH aldehyde), 1666 υ(CH=O), 1624 υ(CH=N), 1576 υ(C=C), 1338 υ(CH of CH_3), 1258 υ(C-N) and 747 υ(C-H bending). ^{1}H NMR (400MHz, $CDCl_3$-d_1) δ (ppm): 14.44 (s, 1H, N*H*), 9.78 (s, 1H, C*H*O), 8.8 (s, 1H, C*H*=N), 8.14-7.25 (Ar-*H*), 2.4 (s, H, CH_3), 1.94 (s, 6H, 2xCH_3). ^{13}C NMR of (100 MHz, DMSO-d_6) δ (ppm): 186.93 (*C*HO)), 185.02(NH-*C*=C), 153 (CH=N), 148.06, 139.32, 137.97, 132.53, 130.03, 129.56, 129.27, 127.99, 125.34, 127.09, 124.77, 123.30, 120.25 and 117.54, (*Ar*-H), 107.47 (C=*C*-CHO, 55.44 (CH_3-*C*-CH_3), 22.21(CH_3-Ar) and 20.76 (2x *C*H_3).

2. 1. 3. 7. Synthesis of 3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal **(7)** as demonstrated in figure (2. 7)



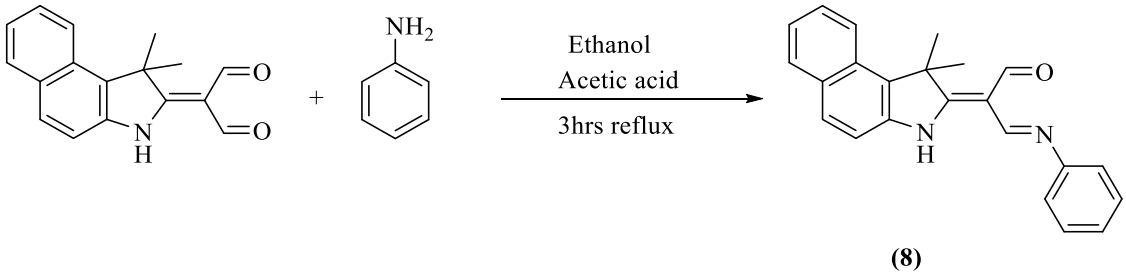
(7)

figure (2. 7): The synthetic pathway of 3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal **(7)**

A solution of (0.5 g, 1.8mmol) of 2-(1,1-dimethyl-2,3-dihydro-benzo[e]indol-2-ylidene)-malonaldehyde **(1)** was dissolved in ethanol 50 ml and (0.228 g, 1.8 mmol) of 4-chloro aniline dissolved in ethanol 20 ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78°C, the progress of the reaction was monitored

by TLC. After 3h the reaction was completed, as indicated by TLC (3:2) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Reduce the solvent. Yellow crystals were formed in the following day, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried over the silica-gel. [81] Yield: (0.59 g, 84%). m.p 165-166 °C. IR data in (cm^{-1}): 3324υ (NH), 3059 υ(CH aromatic), 2975 and 2927 υ(CH aliphatic), 2857 and 2683 υ(CH aldehyde), 1665 υ(CH=O), 1624 υ(CH=N), 1568 υ(C=C), 1321 υ(CH of CH_3), 1237 υ(C-N), 819 υ(C-Cl), 746 υ(C-H bending). ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 14.23 (s, 1H, N*H*), 9.48 (s, 1H, C*H*O), 8.69 (s, 1H, C*H*=N), 8.16-7.48 (Ar-*H*), 1.82 (s, 6H, 2xCH_3). ^{13}C NMR of (100 MHz, DMSO-d_6) δ (ppm): 188.88 (*C*HO)), 185.2 (NH-*C*=C), 157.49 (CH=N), 147.96, 139.32, 137.97, 132.53, 130.03, 129.56, 129.27, 127.99, 125.34, 127.09, 124.77, 123.30, 120.25 and 119.47, (*Ar*-H), 108.97 (C=*C*-CHO, 55.98 (CH_3-*C*-CH_3) and 20.94 (2x *C*H_3).

2. 1. 3. 8. Synthesis of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal (**8**) as illustrated in figure (2. 8)

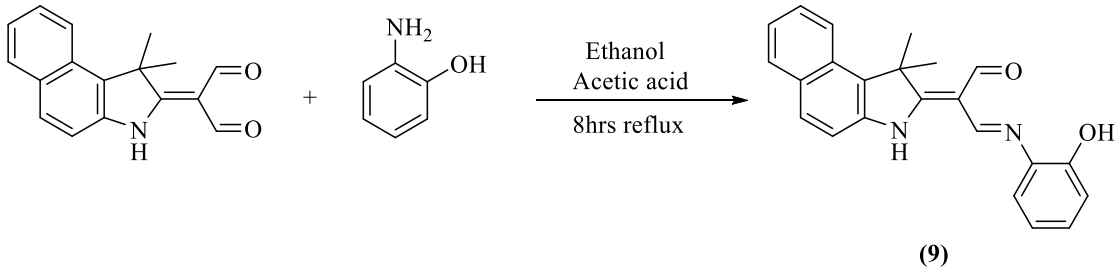


(8)

figure (2. 8): The Synthetic pathway of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal **(8)**

A solution of (0.5 g, 1.8mmol) of 2-(1,1-dimethyl-2,3-dihydro-benzo[e]indol-2-ylidene)-malonaldehyde **(1)** was dissolved in ethanol 50 ml and (0.168 g, 1.8 mmol) of aniline dissolved in ethanol 20 ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78°C the progress of the reaction was monitored by TLC. After 3hrs the reaction was completed, as indicated by TLC (3:2) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Reduce the solvent. Yellow crystals were formed in the following day, flitered off, recrystyled by ethanol to afford pure yellow precipitate and dried over the silica-gel. [81] Yield: (0.53 g, 83%) m.p 153-154 °C. IR data in (cm^{-1}): 3461υ (NH), 3046 υ(CH aromatic), 2970 and 2935 υ(CH aliphatic), 2857 and 2728 υ(CH aldehyde), 1669 υ(CH=O), 1628 υ(CH=N), 1597 υ(C=C), 1338 υ(CH of CH_3), 1258 υ(C-N) and 750 υ(C-H) bending. ^{1}H NMR (400MHz, $CDCl_3$): 14.31 (br, 1H, N*H*), 9.68 (s, 1H, C*H*O), 8.32 (s, 1H, C*H*=N), 8.01-7.15 (Ar-*H*), 1.82 (s, 6H, 2xCH_3). ^{13}C NMR of (100 MHz, DMSO-d_6) δ (ppm): 187.28 (*C*HO)), 185.07(NH-*C*=C), 153.49 (CH=N), 148.00, 140.25, 137.84, 129.91, 129.77, 126.06, 129.09, 126.50, 125.62, 124.27, 122.87, 118.56 and 118.20, (*Ar*-H), 107.84 (C=*C*-CHO, 55.58(CH_3-*C*-CH_3) and 22.46 (2x *C*H_3).

2. 1. 3. 9. Synthesis of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2-hydroxyphenyl)imino) propanal (9) as illustrated in figure (2. 9)

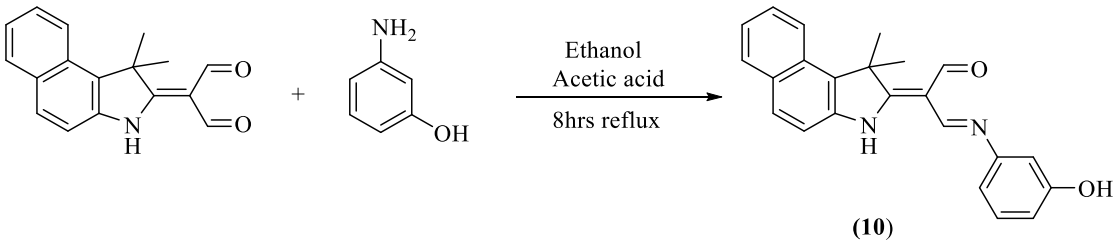


(9)

figure (2. 9): The Synthetic pathway of (2E,3E)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2-hydroxyphenyl)imino)propanal **(9)**

A solution of (0.2 g, 0.75 mmol) of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde **(1)** was dissolved in ethanol 15 ml and (0.08 g, 0.75 mmol) of 2-hydroxy aniline was dissolved in ethanol 10ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 ºC for 8hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. [81] The completion of the reaction was checked by using TLC (3:1) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.24 g, 90%), m.p.154-155ºC. IR data in (cm^{-1}): 3435υ (NH), 3015 υ(CH aromatic), 2927 and 2871 υ(CH aliphatic), 2729 and 2680 υ(CH aldehyde), 1669 υ(CH=O), 1620 υ(CH=N), 1512 υ(C=C), 1341 υ(CH of CH_3), 1272 υ(C-N) and 749 υ(C-H) bending. ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 14.24 (s, 1H, N*H*), 9.77 (s, 1H, C*H*O), 8.70 (s, 1H, C*H*=N), 8.15 (d, 1H, Ar-*H*), 8.02-6.92 (Ar-*H*), 1.82, 1.92 (s, 6H, 2xCH_3).

2. 1. 3. 10. Synthesis of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((3-hydroxyphenyl)imino) propanal **(10)** as illustrated in figure (2. 10)

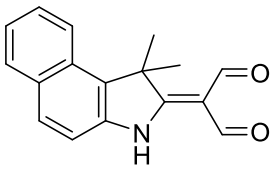
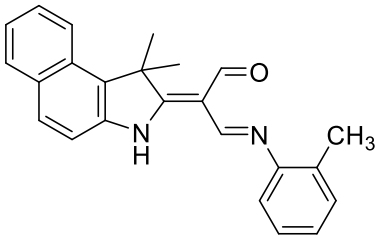
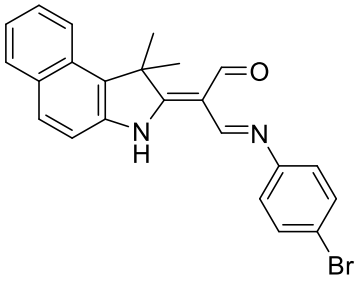
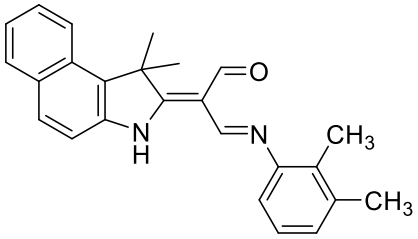
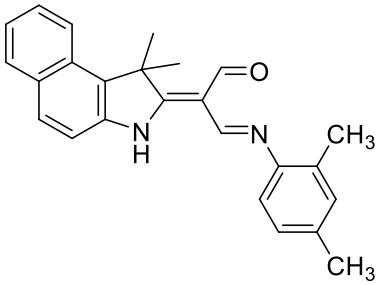


(10)

figure (2. 10): The Synthetic pathway of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((3-hydroxyphenyl)imino)propanal **(10)**

A solution of (0.2 g, 0.75 mmol) of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde **(1)** was dissolved in ethanol 15 ml and (0.08 g, 0.75 mmol) of 3-hydroxy aniline was dissolved in ethanol 10ml and then added glacial acetic acid 2ml to the solution. The mixture was refluxed in a water bath at 78 ºC for 8hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. [81] The completion of the reaction was checked by using TLC (3:1) hexane: ethyl acetate with pre-coated silica gel, which gave one spot. Yield (0.22 g, 82%), m.p.243-244ºC. IR data in (cm^{-1}): 3421υ (NH), 3066 υ(CH aromatic), 2975 and 2941 υ(CH aliphatic), 2723 υ(CH aldehyde), 1669 υ(CH=O), 1613 υ(CH=N), 1519 υ(C=C), 1348 υ(CH of CH_3), 1272 υ(C-N) and 754 υ(C-H) bending. ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 14.1 (s, 1H, N*H*), 9.74 (s, 1H, C*H*O), 8.26 (s, 1H, C*H*=N), 8.15-7.24 (Ar-*H*), 4.2 (s, 1H , OH),1.90 (s, 6H, 2xCH_3).

Table (2. 2): Showed the newly synthesized compounds

Comp. No.	Comp. structure	Comp. name
1		2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde
2		2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(o-tolylimino)propanal
3		3-((4-bromophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal
4		2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal
5		2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,4-dimethylphenyl)imino)propanal

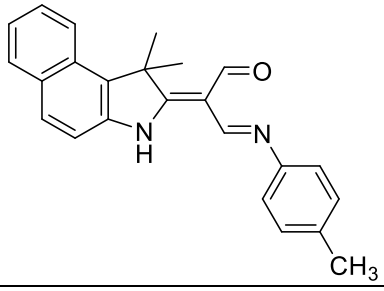
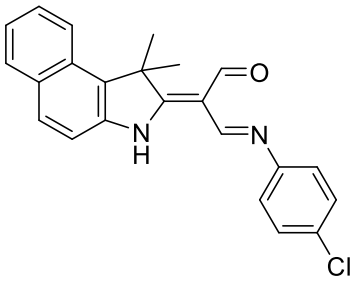
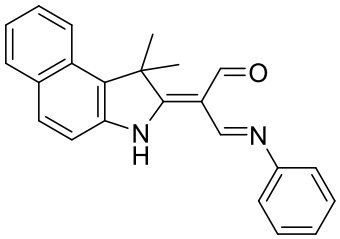
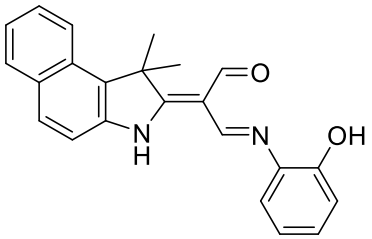
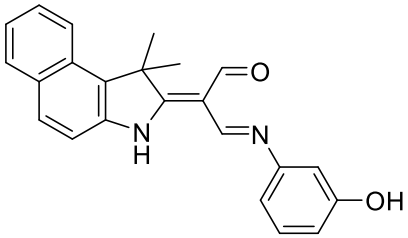
6		2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(p-tolylimino)propanal
7		3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal
8		2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal
9		2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2-hydroxyphenyl)imino)propanal
10		2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((3-hydroxyphenyl)imino)propanal

table (2.3): Physical properties of the synthesized compounds (1-10)

Comp. No.	Molecular formula	Molecular weight	Percentage Yield	Melting Point ºC	Rf
1	$C_{17}H_{15}NO_2$	265.31	98%	202-203	-
2	$C_{24}H_{22}N_2O$	354.45	90%	281-282	0.49
3	$C_{23}H_{19}BrN_2O$	419.32	85%	169-170	0.49
4	$C_{25}H_{24}N_2O$	368.19	80%	211-212	0.31
5	$C_{25}H_{24}N_2O$	368.19	83.5%	152-153	0.47
6	$C_{24}H_{22}N_2O$	354.45	82%	141-142	0.40
7	$C_{23}H_{19}ClN_2O$	374.87	84%	165-166	0.44
8	$C_{23}H_{20}N_2O$	340.43	83%	153-154	0.37
9	$C_{23}H_{20}N_2O_2$	356.43	90%	154-155	0.46
10	$C_{23}H_{20}N_2O_2$	356.43	82%	243-244	0.16

2. 2. Biological part:

2. 2. 1. Materials

All chemicals used in the biological part were obtained from different company suppliers as listed in table (2. 4).

Table (2. 4). Chemicals and solvents used in the biological part

Materials and chemicals	Molecular formula	Company
Benzatin penicillin	-	SDI
Crystal Violate stain	-	BDH
Dimethyl sulfoxide	C_2H_6OS	Aldrich
Methanol	CH_3OH	Scharlaw
Fetal Galf serum	-	Flow lap
potassium chloride	KCl	Merck
Potassium dihydrogen phosphate	KH_2PO_4	BDH
Rosswell Park Memorial Institute-1640 medium (RPMI)	-	Gibco
Sodium Bicarbonate	$NaHCO_3$	BDH
Sodium chloride	NaCl	BDH
Sodium hydrogen phosphate	Na_2HPO_4	Merck
Streptomycin	-	Ajanta

Tripsin/Versene	-	US biological
Trypan Blue stain	-	Pharma

2. 2. 2. Instruments:-

The instruments used in this study are found in Iraqi Center for Cancer and Medical Genetics Research (ICCMGR) / University of Mustansiriya, and their Manufacturers are listed in table (2. 5).

Table (2. 5): Instruments and Manufacturers are used in the biological part

Instrument	Manufacturer
Autoclave	Hospital management (Germany)
CO_2 incubator	Gallenkamp (UK)
Enzyme linked immune absorbent assay reader (Elisa)	Biotek Winooski Elisa (USA)
Hot plate with magnetic stirrer:	Gallenkamp (UK)
Inverted phase contrast microscope CK 40	Olympus (japan)
PH meter	Orient Research (USA)
Vortex	Buchi (Germany)
Water path	précis term (Germany)

2. 2. 3. Preparation methods

2. 2. 3. 1. Solutions preparation for cell culture

2. 2. 3. 1. 1. Antibiotics solution

Two types of antibiotics were added to the culture media, first one was benzathin penicillin (1000000 IU) was dissolved in 10ml of triple distilled water to get a stock solution with 100000 IU. Second antibiotic used was streptomycin and 1gm was dissolved in 5ml triple distilled water to get a stock solution with 200mg/ml. To each 500ml of cell culture media 0.5ml of benzathin penicillin (100000 IU) and 0.25ml of streptomycin (200mg/ml) were added. The final concentration of benzathin penicillin and streptomycin were 100 IU/ml and 100μg/ml of culture media respectively.[82, 83]

2. 2. 3. 1. 2. Sodium Bicarbonate

This solution was prepared according to [84] by dissolving 2.2g of sodium bicarbonate in one liter of culture media.

2. 2. 3. 1. 3. Phosphate buffer saline (PBS)

This buffer was prepared according to [85] by dissolving 8g of NaCl, 0.2g of KCl, 0.92g of Na_2HPO_4 and 0.2g of KH_2PO_4 in one litter of triple distilled water. Stirred constantly on a magnetic stirrer at room temperature then adjust the PH to 7.2. This solution was autoclaved at 121 ºC for 15 min. and stored at 4 ºC until used.

2. 2. 3. 1. 4. Fetal Calf Serum

Bottle that contains serum was water bathed for an hour at 56 ºC, then sterilize it and use directly for culture media.

2. 2. 3. 1. 5. Trypsin/ Versene solution

This solution was prepared according to the manufacturer recommendations by dissolving 10.1g of trypsin/ versene powder

in 900ml triple distilled water plus 1g of sodium bicarbonate and stirred constantly on a magnetic stirrer at room temperature and the volume was completed to one liter. The solution then sterilized by a Nalgene filter unit (0.22μm) and divided into several batches and stored at 4 ºC.

2. 2. 3. 1. 6. Crystal violate stain

Five mg of crystal violate dissolved in 200ml of methanol and 50ml of 37% formaldehyde was prepared and stored at room temperature.

2. 2. 3. 1. 7. Trypan Blue Stain

One g of Trypan Blue was dissolved in 100mL of Phosphate buffer saline (PBS) then filtered with filter paper and the solution was diluted before use in ratio 1:10 with PBS.

2. 2. 3. 2. Tissue Culture Media

2. 2. 3. 2. 1. Rosswell Park Memorial Institute1640 medium (RPMI)

The culture media was prepared as follows:

About 10.4 g of powder medium that contains (HEPES buffer and L-glutamine) was dissolved in approximately 600ml of triple distilled water then the other contains were added gradually:

A) Sodium bicarbonate powder 2.2g

B) Benzyl penicillin 100mg/ml

C) Streptomycin 100 IU/ml

D) Fetal Calf Serum 100ml

The volume was completed to one litter of triple distilled water and then sterilized using Nalgene filter (0.2μm).

2. 2. 3. 3. Compounds stock and diluted concentrations preparations

Solubility assessment of the new synthesized compounds were carried out according to standard test method protocol (The National Toxicology Program). The new chemical compounds (3, 5, 6, 8, 9 and 10) were dissolved in 1ml of Dimethyl sulfoxide (DMSO) and filtered with Millipore filter 0.2 µm, this will represent as stock solutions. From stock solution then prepare the next dilutions by diluted the stock with free serum media to the chosen concentrations (25µg/ml, 50µg/ml and 100µg/ml) for each compounds.

2. 2. 4. Cell lines that used in this project

One type of cell lines were provided by (ICCMGR).

2. 2. 4. 1. Infiltrating Ductal Carcinoma AMJ 13

This cell line was established from primary tumor of 70 years old Iraqi woman was diagnosed histologically with infiltrating ductal carcinoma and is named as AMJ13 according to (Ahmed Majed Jabrea 2013, and the year in which the cell line was established). The cells were morphologically characterized by light and scanning electron microscopy and shown to be elongated multipolar epithelial-like cells with a population doubling time of 22h. [86]

2. 2. 5. Cell line maintenance:

Cell lines were maintained to grow continuously; to do this confluent cell lines were sub-cultured by decanting the medium off

and cells washed with 1ml PBS. From trypsin/ versin solution 0.5ml was added to the last washed cells and waiting 3-5 min. until the cells started detach from the falcon. Cells were dispensed in growth medium and incubated with 5% CO_2 at 37 ºC. [87]

2. 2. 6. Cytotoxicity assay on tumor cell line

The effect of the six chemical compounds and their dilutions on ductal carcinoma AMJ13 cell line was measured by cytotoxicity assay using 96-well micro titration plat as described by the method of. [88]

2. 2. 6. 1. Cells seeding

cell line (AMJ13) was treated as described in (2. 2. 6) to get cell suspension. Each well of 96- well plate was seeded with 100μl (10^4 cell/ well) from the cell suspension, then the cover of the plate was placed on and contoured with parafilm and placed in the incubator 5% CO_2 for 24h. at 37 ºC.

2. 2. 6. 2. Exposure

The 96- well plate was divided to seven groups, six of the wells were including six compounds with their three concentrations in triplicate, the seventh one was for control untreated cells. Before exposure of the compounds, media was decanted from the seeded cells by micropipette. Each row represent a chemical compounds with its concentration in three replicates, 200μl of each concentration of specific chemical compounds were added to the seeded cells' well. The control cells untreated with the chemical compounds were treated with free serum media. The plate was

covered again and sealed with parafilm and placed in the incubator at 37 ºC with 5% CO_2. [89]

2. 2. 6. 3. Cytotoxicity evaluation

The effect of the tested chemical compounds on was measured after 48 h. of exposure. Cell viability was measured by removing the media from the plate and adding 200μl of crystal violate and replace it in the incubator for 20 min at 37 ºC. After extensive washes with water, plates were air-dried and absorbance measured at 560–600nm on a spectrophotometric micro plate reader. Cell adhesion or growth inhibition was expressed as percentage of control cells as the following equation:

$$\text{Inhibition Rate \%} = \frac{\text{mean abs.of control wells} - \text{mean abs.of treated concentration}}{\text{mean abs.of control wells}} \times 100$$

CHAPTER THREE

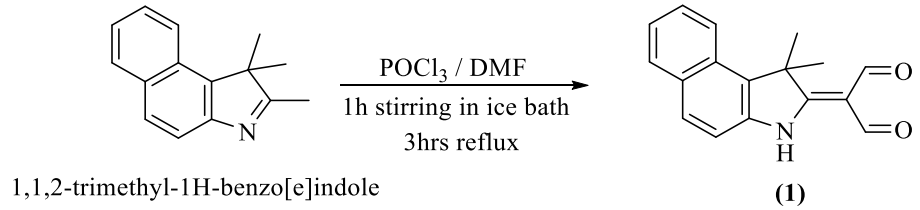
RESULT AND DISCUSSION

3. Results and discussion

3. 1. Chemistry Part

3. 1. 1. Methodology

The compound 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde (1) was synthesized by Vilsmier Haack reaction, in which (1,1,2-trimethyl-1H-benzo[e]indole) reacts with Phosphoryl chloride ($POCl_3$) in presence of *N*,*N*-dimethyl formamide (DMF),[90] as shown in Scheme (3. 1), this compound (1) reacts with different Substituted Aniline in ratio (1:1) to form our new compounds (2-10) by the condensation reaction.



1,1,2-trimethyl-1H-benzo[e]indole **(1)**

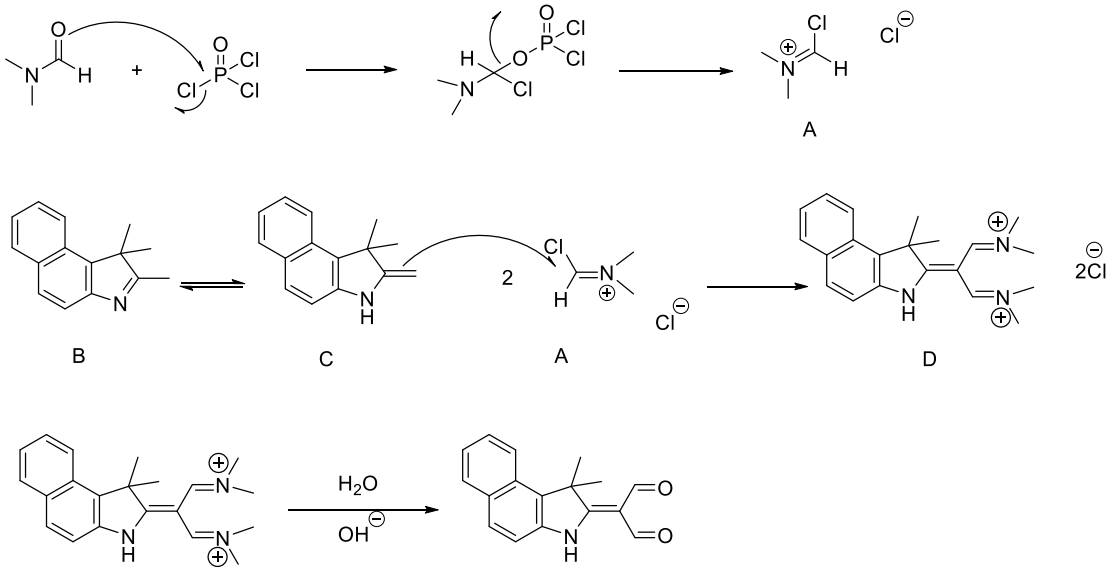
scheme (3. 1): Synthetic pathway of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde (1)

The suggested mechanism of the formation 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde (1) involves three steps as proposed by [91,92] as shown in Scheme (3. 2).

In the first step: combination of DMF with $POCl_3$ to formation of chloroiminium ion (A).

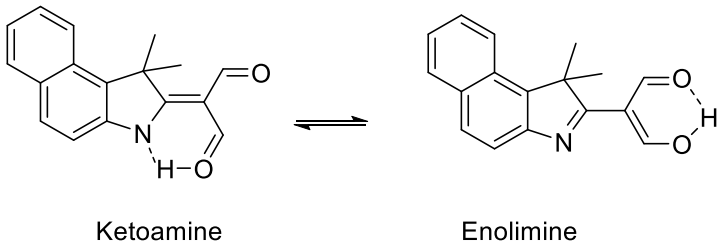
In the second step: reaction of chloroiminium ion A with1,1,2-trimethyl-1H-benzo[e]indole (B), that going to be in the equilibrium with enamine tautomer C. latter the chloroiminium ion form the first step was attacks, to create the intermediate D.

In the third step: hydrolysis of intermediate D, to produce E, 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde (1).



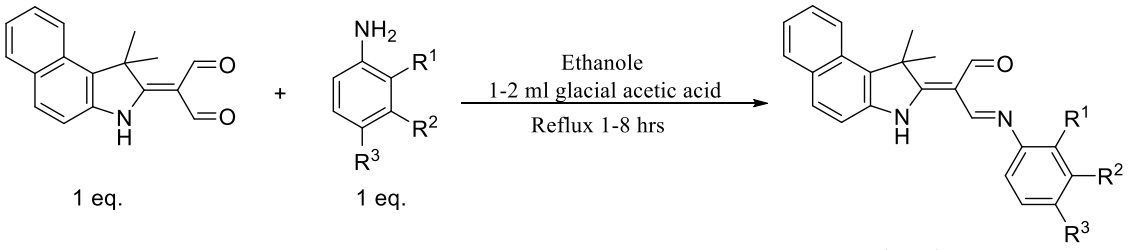
scheme (3. 2): Mechanism of Vilsmier reaction to form the compound (1)

This compound was found as ketoamine-enolimine tautomer forms [93,94] as shown in scheme (3. 3)



scheme (3. 3): Tautomer forms of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde (1)

A series of new compounds have been synthesized from 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene) malonaldehyde **(1)** by the condensation reaction of this compound with substituents of aniline according to synthetic pathway as shown in scheme (3. 4).

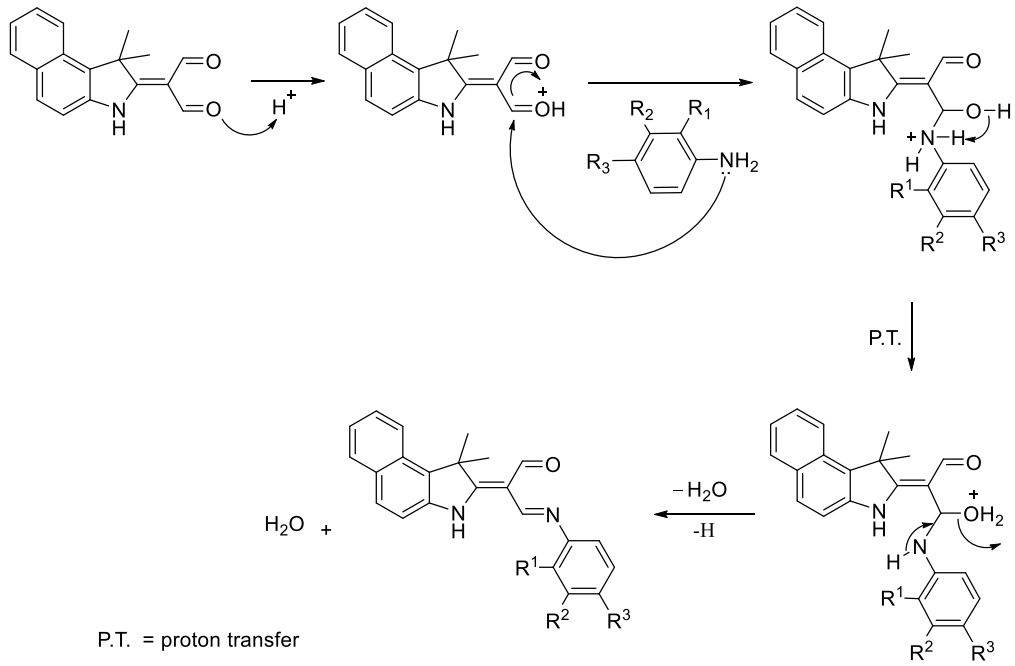


(2-10)

Comp. no.	R^1	R^2	R^3	Time
2	CH_3	H	H	1 h
3	H	H	Br	4 h
4	CH_3	CH_3	H	3 h
5	CH_3	H	CH_3	5 h
6	H	H	CH_3	4 h
7	H	H	Cl	3 h
8	H	H	H	3 h
9	OH	H	H	8 h
10	H	OH	H	8 h

scheme (3. 4): Synthetic pathway of compounds (2-10)

The mechanism for the formation of the synthesized compounds are illustrated in the scheme (3. 5). [50]



scheme (3. 5): Mechanism of the synthesized compounds (2-10)

The last new synthesized compound (1) was used to synthesize new compounds, all new synthesized compounds are colored, stable in the air and not soluble in water and hexane. Their purities have been tested by TLC and their chemical structures have been confirmed by spectroscopic technique such as FT-IR and ^{1}HNMR, APT ^{13}C NMR as well as their physical properties like, melting points were determenined. Also percentage yield of the new compounds are represented in table (2. 3). The results of all new synthesized compounds are discussed below.

3. 1. 2. Spectral study of the new synthesized compounds(2-10)

3. 1. 2. 1. FT-IR Study

The results of the FTIR Spectrum for the new synthesized compounds displayed absorption bands in range between 400 - 4000 cm^{-1}.

The new compounds (2-10) showed disappeared the absorption bands of (NH_2) group which belonged to substituted anilines and showed new absorption bands of imine groups (CH=N) so that approved to formation of these new compounds. Also some of these new compounds (2-10) don't showed absorption bands was attributed to (NH) group for indole ring because of these new compounds are stabilized by intramolecular N-H…N and N-H…O hydrogen bonds.

FT-IR for the compound 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal (4).

This compound was prepared by reaction of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde and 2,3-dimethylaniline in ethanol with glacial acetic acid as a catalyst.

The FT-IR spectra of this synthesized compound figure (3. 1) display absorption band at 3447 cm^{-1} was belonged to (N-H), 3053 cm^{-1} was assigned to aromatic (C-H), 2963 and 2928 cm^{-1} were assigned to and aliphatic (C-H) [95], also absorption bands at 2866 and 2707 cm^{-1} were belonged to (C-H) aldehyde, the strong absorption band at 1662 cm^{-1} was belonged to the carbonyl group (C=O). [96] and at 1617 cm^{-1} for azomethine group (CH=N), the new functional group which was indicated and approved to the formation of this compound.[97] As well as stretching frequency at 1579cm^{-1} was referred to(C=C) group [98], at the same time the absorption bands was appeared at 1338cm^{-1} was belonged to the CH_3 group [99], also The absorption band at 1272cm^{-1} which

attributed to (C-N) groups [100], and finely A sharp peak at 771cm^{-1} is attributed to out -of-plane (C-H) group .[101]

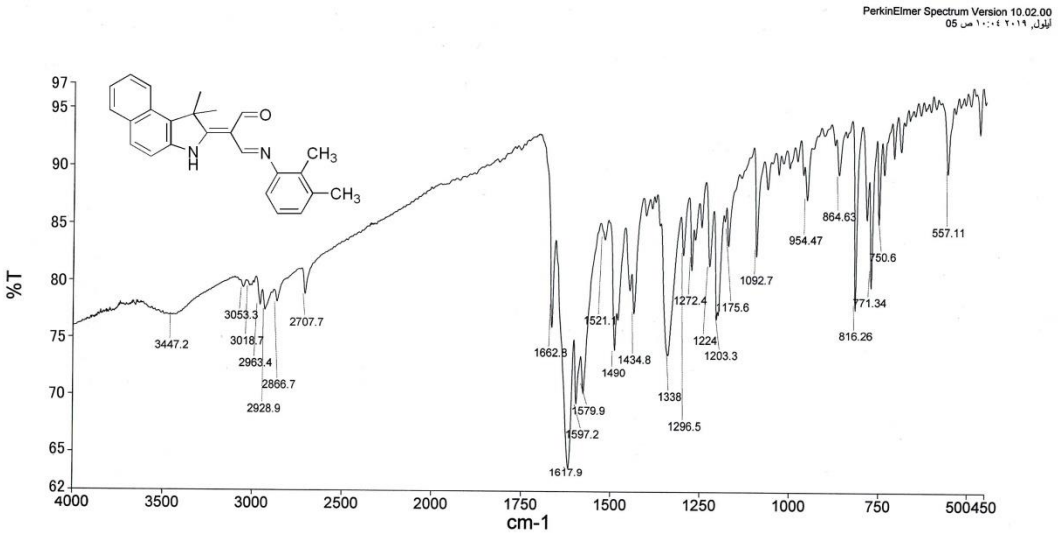


figure (3. 1): The FTIR spectra of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal (4)

FT-IR for the compound 3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal (7)

This compound was prepared by reaction of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde and 4-chloro aniline in ethanol with glacial acetic acid as a catalyst.

The FT-IR spectra of this synthesized compound figure (3. 2) display absorption band at 3324 cm^{-1} was belonged to (N-H), 3059 cm^{-1} was assigned to aromatic (C-H), 2975 and 2927 cm^{-1} were assigned to aliphatic (C-H), also absorption bands at 2857 and 2683 cm^{-1} was belonged to (C-H) aldehyde, the strong absorption band at 1665cm^{-1} was belonged to the carbonyl group (C=O) and at 1624 cm^{-1} for azomethine group (CH=N), the new functional group which was indicated and approved to the formation of this compound. As well as stretching frequency at 1568cm^{-1} was referred to(C=C) group, at the same time the absorption bands was

appeared at 1321 cm^{-1} was belonged to the CH_3 group, also The absorption band at 1237 cm^{-1} which attributed to (C-N) group ، a peak at 819 cm^{-1} was attributed to (C-Cl) group. And finely A sharp peak at 746 cm^{-1} is attributed to out -of-plane (C-H) group of aromatic ring.

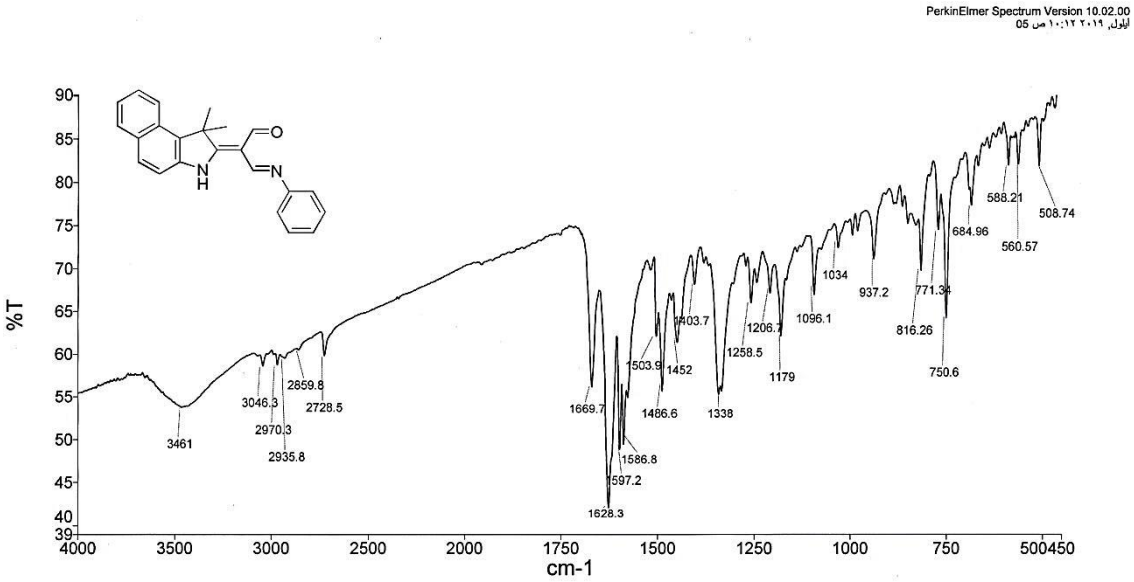


figure (3. 2): The FTIR spectra of 3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal (7)

FT-IR for the compound 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal (8). This compound was prepared by reaction of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde and aniline in ethanol with glacial acetic acid as a catalyst.

The FT-IR spectra of this synthesized compound figure (3. 3) display absorption band at 3461 cm^{-1} was belonged to (N-H), 3046 cm^{-1} was assigned to aromatic (C-H), 2970 and 2935 cm^{-1} for aliphatic (C-H), also absorption bands at 2859 and 2728 cm^{-1} were belonged to (C-H) aldehyde, the strong absorption band at 1669cm^{-1} was belonged to the carbonyl group (C=O) and at 1628 cm^{-1} for azomethine group (CH=N), the new functional group which was

indicated and approved to the formation of this compound. As well as stretching frequency at 1597 cm^{-1} was referred to(C=C) group, at the same time the absorption bands was appeared at 1338 cm^{-1} was belonged to the CH_3 group, also The absorption band at 1258 cm^{-1} which attributed to (C-N) group. And finely A sharp peak at 750 cm^{-1} is attributed to out -of-plane (C-H) group of aromatic ring.

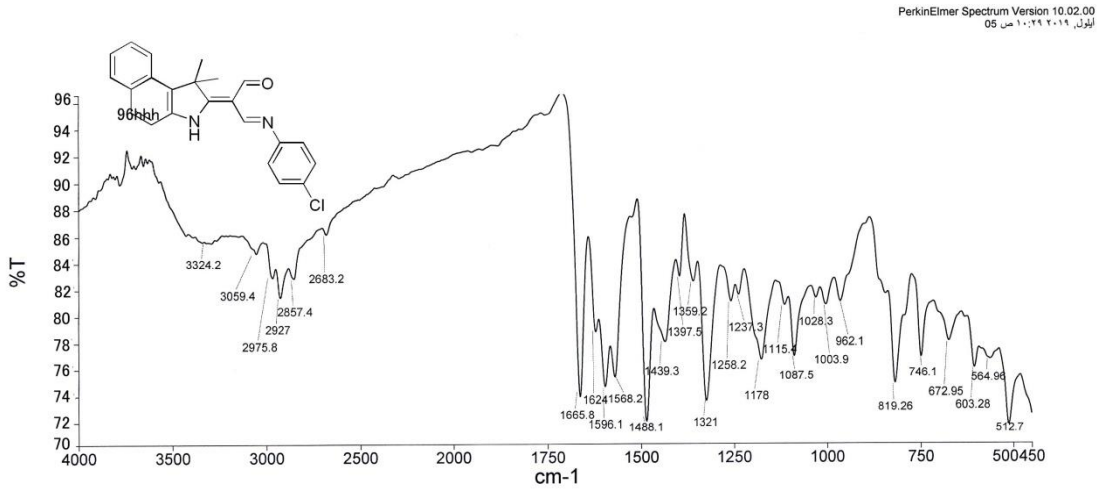


figure (3. 3): The FTIR spectra of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal (8)

The FTIR value for the synthetic compounds are listed in table (3. 1).

table (3. 1): FT- IR spectra for the synthetic compounds

Com. No.	Characteristic band of(FT- IR) spectra (cm^{-1})										
	N-H	C-H ar.	C-H aliph.	C-H ald.	C=O	C=N	C=C	CH_3	C-N	C-H bend.	others
2	3453	3054	2965 and 2930	2866 and 2725	1666	1624	1598	1328	1269	749	-
3	-	3054	2971 and 2930	2866 and 2683	1663	1619	1569	1325	1240	746	(C-Br)) 817
4	3447	3053	2963 and 2928	2866 and 2707	1662	1617	1579	1338	1272	771	-
5	3454	3046	2984 and 2922	2866 and 2721	1669	1624	1579	1334	1255	743	-

6	-	3025	2970 and 2928	2866 and 2694	1666	1624	1576	1338	1258	747	-
7	3324	3059	2975 and 2927	2857 and 2683	1665	1624	1568	1321	1237	746	(C-Cl) 819
8	3461	3046	2970 and 2935	2859 and 2728	1669	1628	1597	1338	1258	750	-
9	3435	3015	2927 and 2871	2729 and 2680	1669	1620	1512	1341	1272	749	-
10	3421	3066	2975 and 2941	2723	1666	1613	1519	1348	1272	754	-

3. 1. 2. 2. NMR Study

^{1}H-NMR and APT ^{13}C-NMR spectra were reported in duterated chloroform ($CDCl_3$) and some of them in duterated DMSO with chemical shifts in ppm and using TMS (tetramethylsilane) as standard.

^{1}H-NMR results of the newly synthesized compounds (2-10) showed disappearance signals and appearance of new signals. Such as disappearance of one proton atom of the carbonyl group and disappearance a signal of NH_2 group on spectrum of substituted anilines and appearance new signal of one proton atom of imine group.

This is approval to the formation of the new compounds. Also the signals of protons of aromatic ring were represented the number of protons that belong for each new compound.

3. 1. 2. 2. 1. ^{1}H-NMR and APT ^{13}C-NMR results of the compound 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal (4).

The ^{1}H-NMR results for compound (4) figure (3. 4) displayed single signal at 14.55 ppm was belonged to proton of (NH) of indole ring.[102] A singlet signal at 9.70 ppm was referred to the one proton atom of carbonyl group (C=O) and single signal at 8.37 ppm was attributed to proton of Schiff base group (CH=N).[103] A signals were appeared in the region between (8.08-7.02) ppm were belonged to nine protons of aromatic ring for compound (4).[104,105] A signal at (2.46 and 2.35) ppm which attributed to two CH3 group. And finally signal at 1.89 ppm was belonged to six protons of two methyl groups.[106]

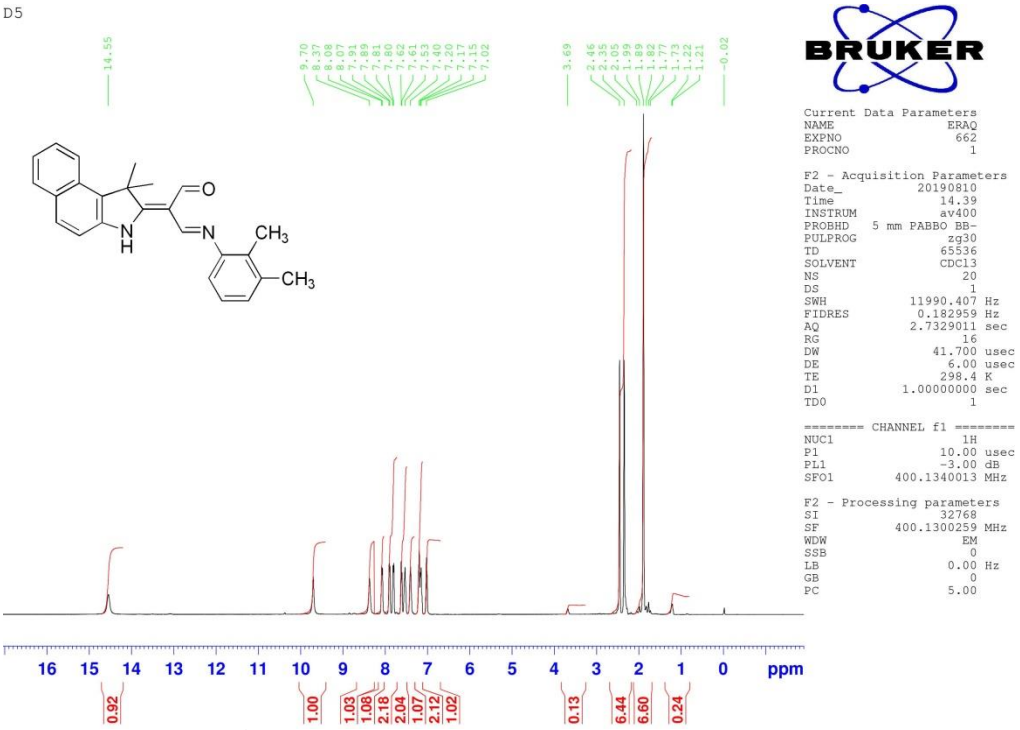


figure (3. 4): ^{1}H-NMR spectrum of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal (4)

APT^{13}C-NMR results were used to characterize this new compound and support the results of ^{1}H-NMR . figure (3. 5)

displayed signals for the quaternary carbons and methylene CH_2 group appeared at a positive side (above of the spectrum). While carbons of CH and CH_3 groups observed at a negative side (below of the spectrum). A signal at 187.36 ppm and 185.47 ppm were assigned to the carbonyl group *C*=O and to NH-C=C group respectively ,[107] while a signal of CH=N group detected at 148.48 ppm. [108] The signals were appear in the range between 138.94-113.99 ppm were belonged to the carbon atoms of aromatic rings. [109] In addition, two signals appeared at 108.37 ppm and 55.85 ppm were assigned to O=C-*C* and CH_3-*C*-CH_3 groups respectively. [110] Signals at (22.41 and 20.75) ppm belongs to two methyl groups at positions *ortho* and *meta* of benzene ring. Finally, signal at 14.09 ppm was belongs to the two methyl groups.[111]

All these results found the 1H-NMR and APT^{13}C-NMR spectrum matched well with the expected signals and was regular with the formation of this new compound.

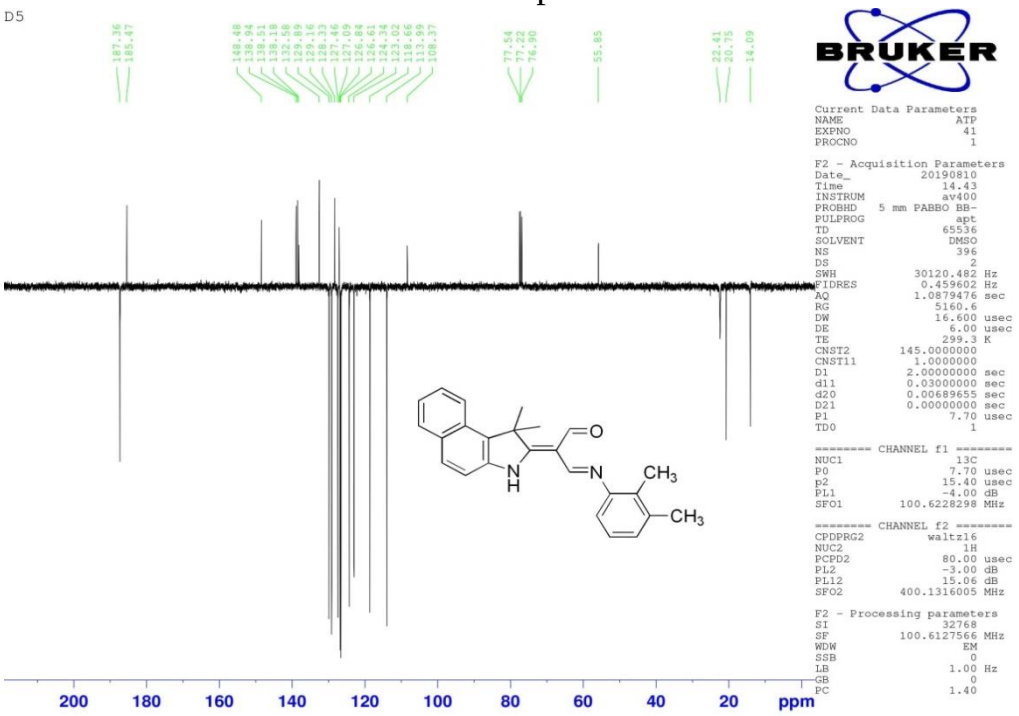


figure (3. 5): APT ^{13}C NMR spectrum of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal (4)

3. 1. 2. 2. 2. ^{1}H-NMR and APT ^{13}C-NMR results of the 3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal (7).

The ^{1}H-NMR results for compound (7) figure (3. 6) displayed single signals at 14.23 ppm was belonged to proton of (NH) of indole ring. A singlet signal at 9.48 ppm was referred to proton atom of carbonyl group (C=O) and single signal at 8.70 ppm was attributed to proton of Schiff base group (CH=N). Also signals were appeared in the region between (8.67-7.48) ppm were belonged to protons of aromatic ring.[(112)] Finally peak at 1.82 ppm was belonged to six protons of two methyl groups.

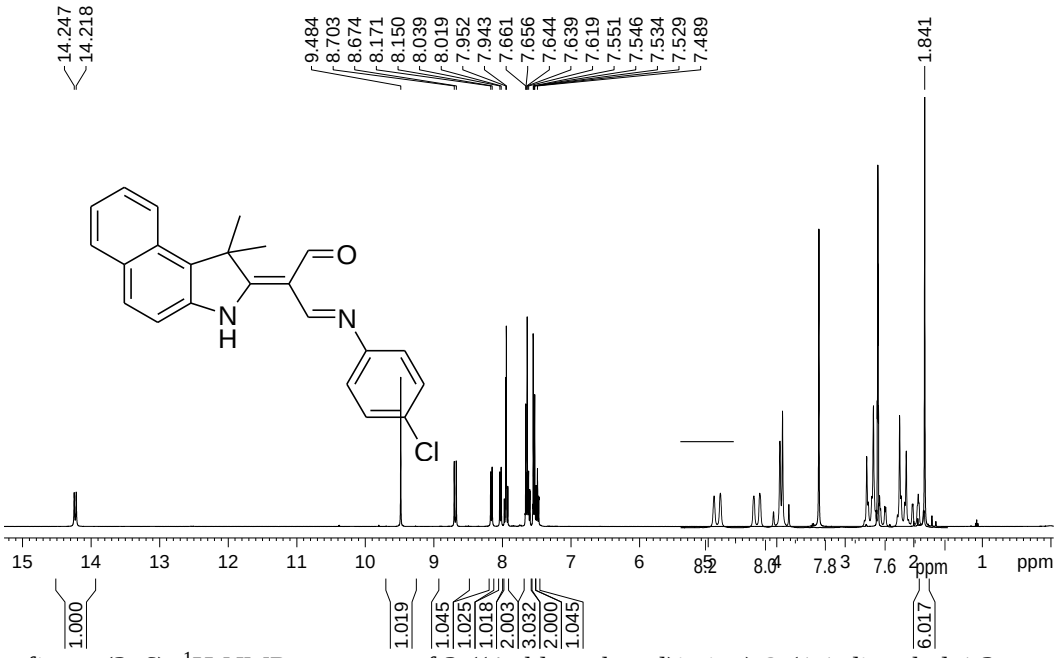


figure (3. 6): ^{1}H-NMR spectrum of 3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal (7).

^{13}C NMR results were supported the ^{1}H NMR results figure (3. 7). This compound show a signal at 188.88 ppm and 185.2 ppm were assigned to the carbonyl group *C*=O and to NH-C=C group respectively, while a signal of CH=N group detected at 157.49 ppm. The signals were appear in the range between 147.96-119.47 ppm were belonged to the carbon atoms of aromatic rings. In

addition, two signals appeared at 108.97 ppm and 55.981 ppm were assigned to O=C-*C* and CH_3-*C*-CH_3 groups respectively. Also a signal at 20.94 ppm was belongs to the two methyl groups. (113)

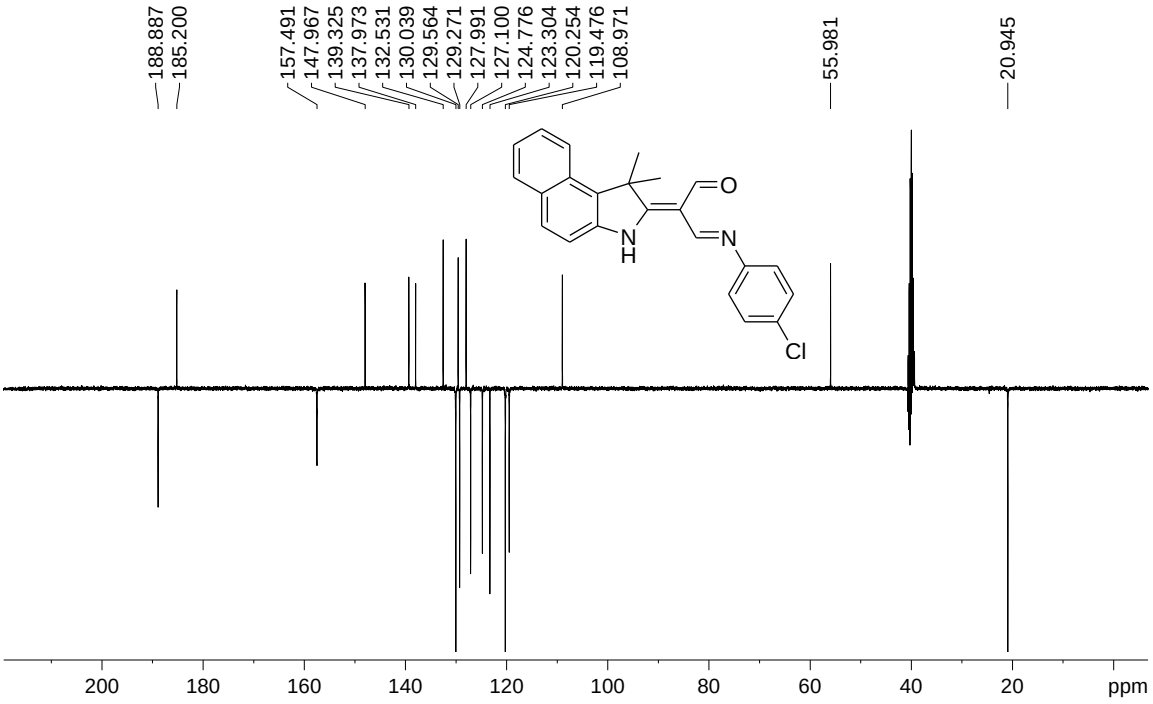


figure (3. 7): APT ^{13}C NMR spectrum of 3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal (7).

3. 1. 2. 2. 3. ^{1}H-NMR and APT ^{13}C-NMR results of the 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal (8)

The ^{1}H-NMR results for compound (8) figure (3. 8) displayed single signals at 14.31 ppm was belonged to proton of (NH) of indole ring. A singlet signal at 9.68 ppm was referred to proton atom of carbonyl group (HC=O) and single signal at 8.32 ppm was attributed to proton of Schiff base group (CH=N). Also signals were appeared in the region between (8.01-7.15) ppm were belonged to protons of aromatic ring.(114) Finally peak at 1.82 ppm was belonged to six protons of two methyl groups.

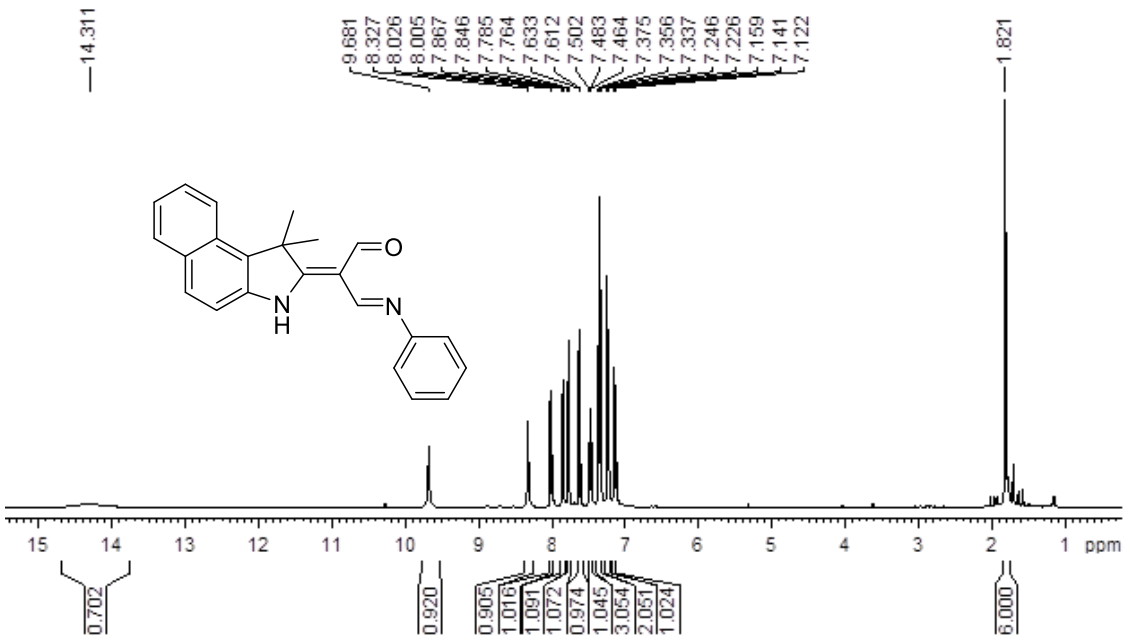


figure (3. 8): ^{1}H-NMR spectrum of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal (8).

^{13}C NMR results were supported the ^{1}H NMR results (Figure 3. 9). A signal at 187.28 ppm and 185.07 ppm were assigned to the carbonyl group *C*=O and to NH-C=C group respectively , while a signal of CH=N group detected at 153.49 ppm . The signals were appear in the range between (148.00 -118.20) ppm were belonged to the carbon atoms of aromatic rings. In addition, two signals appeared at 107.84 ppm and 55.58 ppm were assigned to O=C-*C* and CH_3-*C*-CH_3 groups respectively. Finally, signal at 22.46 ppm was belongs to the two methyl groups.

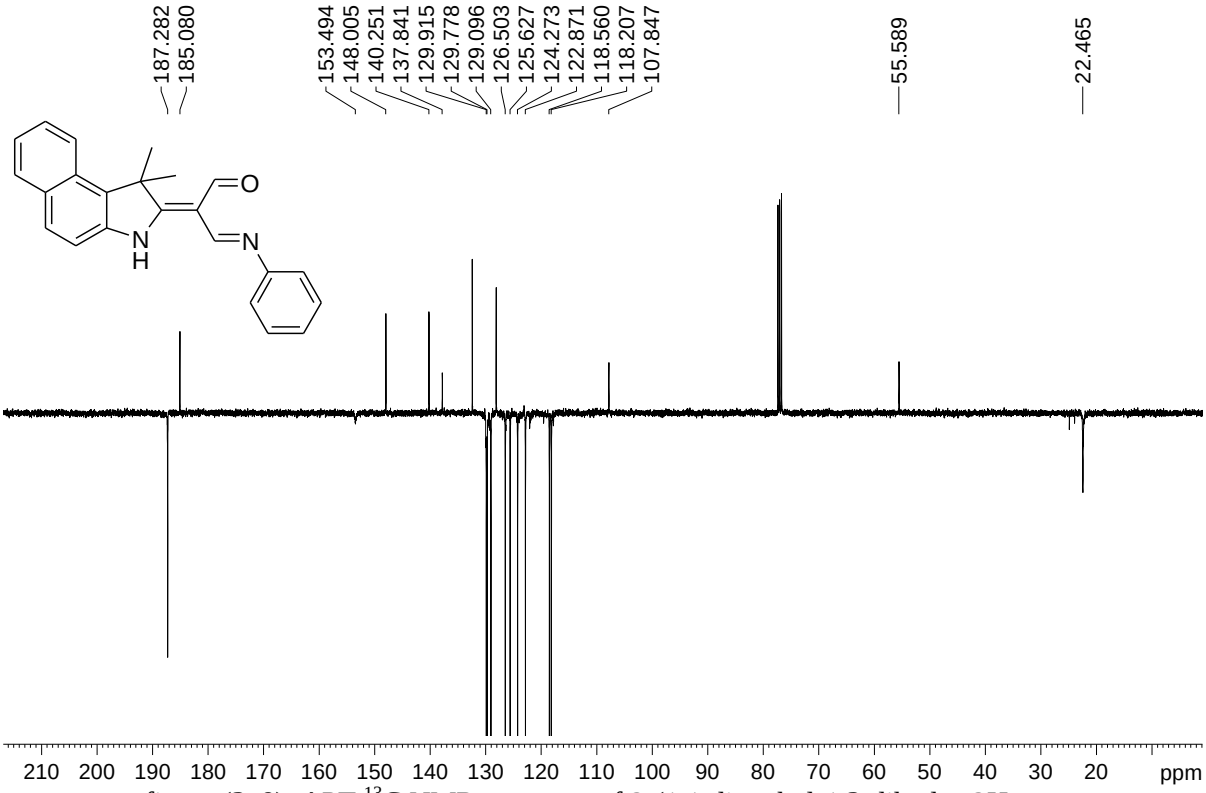


figure (3. 9): APT ^{13}C NMR spectrum of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal (8).

The ^{1}H NMR results of the synthetic new compounds are listed in table (3. 2).

table (3. 2): The chemical shift in ppm to ^{1}H NMR results for the synthetic compounds

Com.No	NH-	HC=O	HC=N	Ar-H	*Ortho* CH_3	*Meta* CH_3	*Para* CH_3	6H,2xCH_3	Other
2	14.59	9.7	8.4	8.11-7.22	2.2	-	-	1.8	-
3	14.44	9.75	8.33	8.07-7.11	-	-	-	1.87	-
4	14.55	9.70	8.37	8.08-7.02	2.35	2.46	-	1.89	-
5	14.49	9.70	8.35	8.08-7.04	2.3	-	2.49	1.91	-
6	14.44	9.78	8.80	8.14-7.25	-	-	2.4	1.94	-

7	14.23	9.48	8.69	8.17-7.48	-	-	-	1.82	-
8	14.31	9.68	8.32	8.01-7.15	-	-	-	1.82	-
9	14.24	9.77	8.70	8.15-6.92	-	-	-	1.92, 1.82	OH 9.43
10	14.1	9.74	8.26	8.15-7.24	-	-	-	1.90	-

The ^{13}C NMR results of the new synthetic compounds are listed in table (3. 3).

table (3. 3): The chemical shift in ppm to the ^{13}CNMR for the synthetic compounds

Com. No.	*C*=O	NH-*C*=C	*C*H=N-	Ar-*C*H	O=C-*C*	CH_3CCH_3	2x CH_3	Other
2	186.57	184.49	152.3	147.5-114.71	107.84	55.03	17.87	*ortho* CH_3 21
3	187.05	184.35	153	146.93 - 118.01	108.07	55.30	22.69	-
4	187.36	185.47	148.48	138.94 - 113.99	108.37	55.85	14.09	*ortho* CH_3 20.75 *meta* CH_3 22.41
5	187	185.27	153	148.35 -115	107.99	55.63	18.06	*ortho* CH_3 20.76 *para* CH_3 22.16
6	186.93	185.02	153	148.06 - 117.54	107.47	55.44	20.76	*Para* CH_3 22.21
7	188.88	185.2	157.49	147.96 - 119.47	108.97	55.981	20.945	-
8	187.28	185.07	153.49	148-118.20	107.84	55.58	22.46	-

3. 2. Biological part

3. 2. 1. Cytotoxicity assay

prepare the concentrations of the six new indole Schiff bases compounds: these compounds were air-stable for extended periods and soluble in dimethyl formamide and DMSO. For this reason we added amount of DMSO and then added RPMI medium slightly to prepare the concentrations (25, 50 and 100µg/ml).

3. 2. 1. 1. Cytotoxicity toward AMJ cell line

Cancer cell line AMJ were seeded as $2*10^4$ cells / well in 96 well plats and after 24 h. when the cells become confluent monolayer, they were exposed to the compound's concentrations at 25, 50 and 100 µg/ml and incubated in 37℃ for 48 h, then stained with crystal violate dye and calculated the inhibition rate (%) for each compound.

3. 2. 1. 1. 1. The cytotoxicity of 3-((4-bromophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal (3).

This compound showed a good cytotoxic inhibition rate after 48 h. of exposure to AMJ cancer cell line at concentrations 25, 50 and 100 µg/ml were 49, 48.3 and 50.3% respectively. Concentration 100 µg/ml represent the ideal concentration prepared from compound (3) that inhibited 50.3% of AMJ cell line after 48 h. as presented below in figure (3. 10).

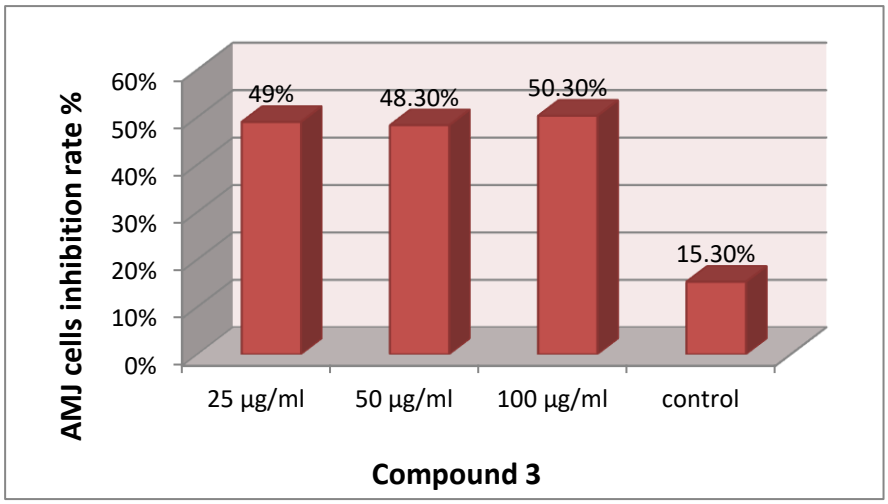


figure (3. 10): AMJ cell line treated with compound (3) concentrations (25, 50 and 100) µg/ml for 48 hours

3. 2. 1. 1. 2. Cytotoxic activity of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,4-dimethylphenyl)imino)propanal (5)

The resultes of compound (5) and its concetrations 25, 50 and 100 µg/ml were illustrated in figure (3. 11) that showed their dependence on concentration at 48h. The inhibition rates were 49, 55.5 and 52.9 % for 48 h.

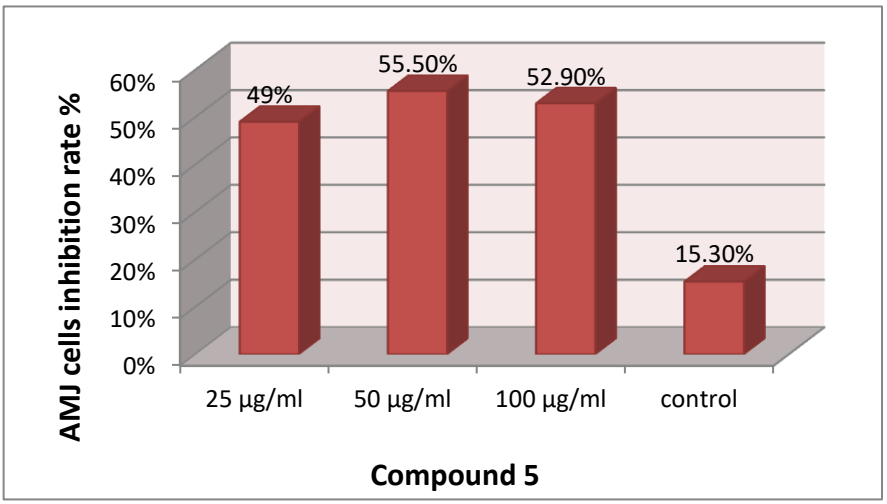


figure (3. 11): AMJ cell line treated with compound (5) concentrations (25, 50 and 100) µg/ml for 48 hours

3. 2. 1. 1. 3. Cytotoxic activity of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(p-tolylimino)propanal (6)

The results of this compound and its concentrations According to figure (3. 12). The concentration 25 and 50 µg/ml have 42 and 36.6 % inhibition rates respectively after 48h to AMJ cells exposure. While the concentration 100 µg/ml has 47.7 % inhibition rates respectively after 48h to AMJ cells exposure.

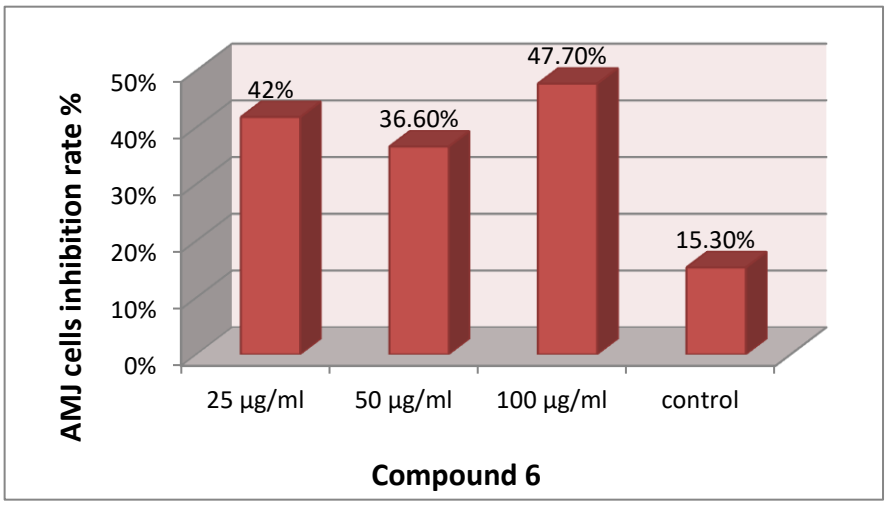


figure (3. 12): AMJ cell line treated with compound (6) concentrations (25, 50 and 100) µg/ml for 48 hours

3. 2. 1. 1. 4. Cytotoxic activity of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal (8)

The results of this compound and its concentrations According to figure (3. 13), determined that the higher concentrations represented the ideal concentrations prepared from this compound. This compound showed a higher cytotoxic inhibition rate after 48 h of exposure to AMJ cancer cell line at concentrations 25, 50 and 100 µg/ml were 41, 57.5, 67.9% respectively. The concentration 100 µg/ml of this compound showed the highest inhibition rate among rest of the tested compounds.

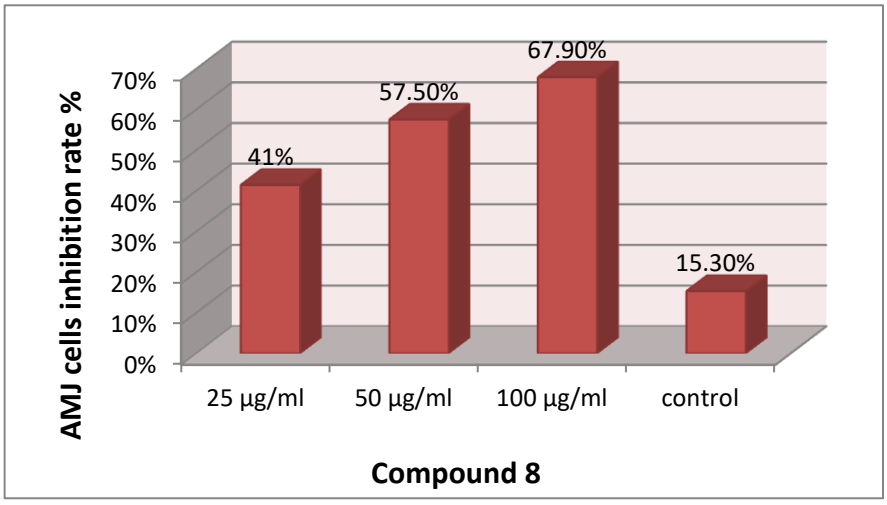


figure (3. 13): AMJ cell line treated with compound (8) concentrations (25, 50 and 100) µg/ml for 48 hours

3. 2. 1. 1. 5. Cytotoxic activity of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2-hydroxyphenyl)imino)propanal (9)

The resultes of compound (9) and its concetrations 25, 50 and 100 µg/ml were illustrated in figure (3. 14) that showed their dependence on concentration at 48h. The inhibition rates were 31, 48.3 and 54.4 % for the concentrations 25, 50 and 100 µg/ml respectively.

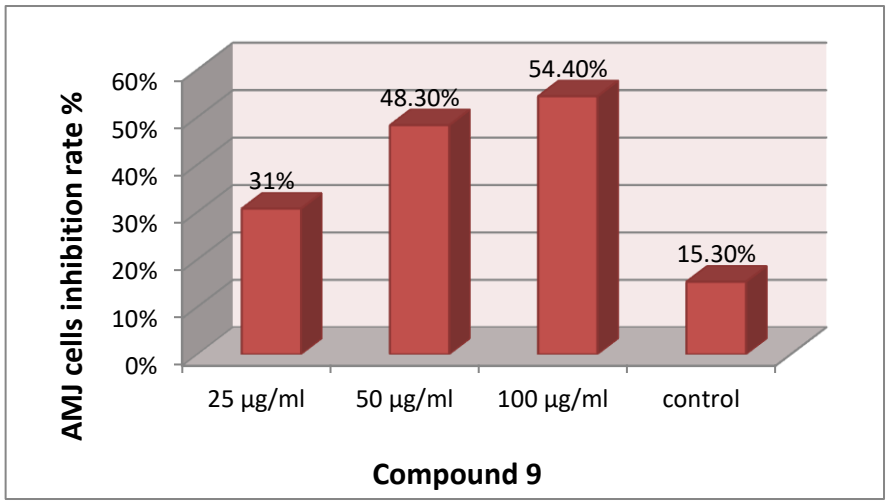


figure (3. 14): AMJ cell line treated with compound (9) concentrations (25, 50 and 100) µg/ml for 48 hours

3. 2. 1. 1. 6. Cytotoxic activity of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((3-hydroxyphenyl)imino)propanal (10)

The inhibition of this compound and its dilutions was showed in figure (3. 15). The concentrations 25, 50 and 100 μg/ml in 48 h. of exposure time that inhibited AMJ cell lines growth with inhibition rates 48, 49 and 40.5% .

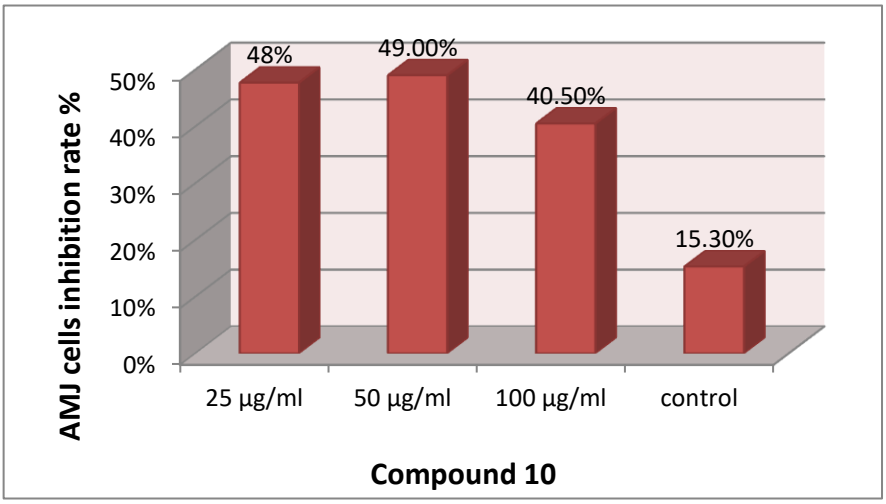


Figure (3. 15): AMJ cell line treated with compound (10) concentrations (25, 50 and 100) µg/ml for 48 hours

Conclusion

In the present work New derivatives indole based Schiff bases were synthesized and identified by spectral methods (FT-IR, ^{1}H, APT ^{13}C-NMR). The synthesized compounds are :

1- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(o-tolylimino) propanal

2- 3-((4-bromophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal

3- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal

4- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,4-dimethylphenyl)imino)propanal

5- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(p-tolylimino)propanal

6- 3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal

7- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal

8- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2-hydroxyphenyl)imino)propanal

9- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((3-hydroxyphenyl)imino)propanal

Six of the synthesized compounds with different concentrations 25, 50, 100 µg/ml were evaluated for their anticancer activity against AMJ-13 breast cancer cell line. Most of the tested showed good

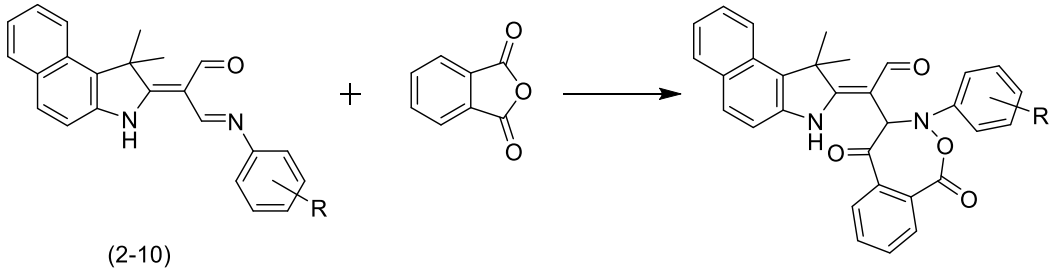
cytotoxity against used cell line and the compound (8) with concentration 100 µg/ml showed highest inhibition rate 67.9 % among rest of the compounds with different concentrations.

Future work

The aim of present work was to synthesis new indole based Schiff bases. But due to lack of time for the planned work, the objective was achieved as a part and rest is being planned to do in the future.

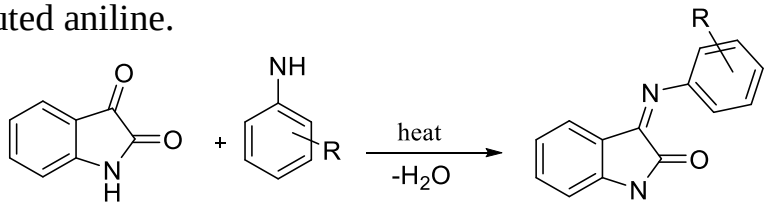
Our plan for the future is to :

1-Synthesis of new derivatives by reacting the synthesized Schiff bases with phthalic anhydride as shown below in scheme(3. 6).

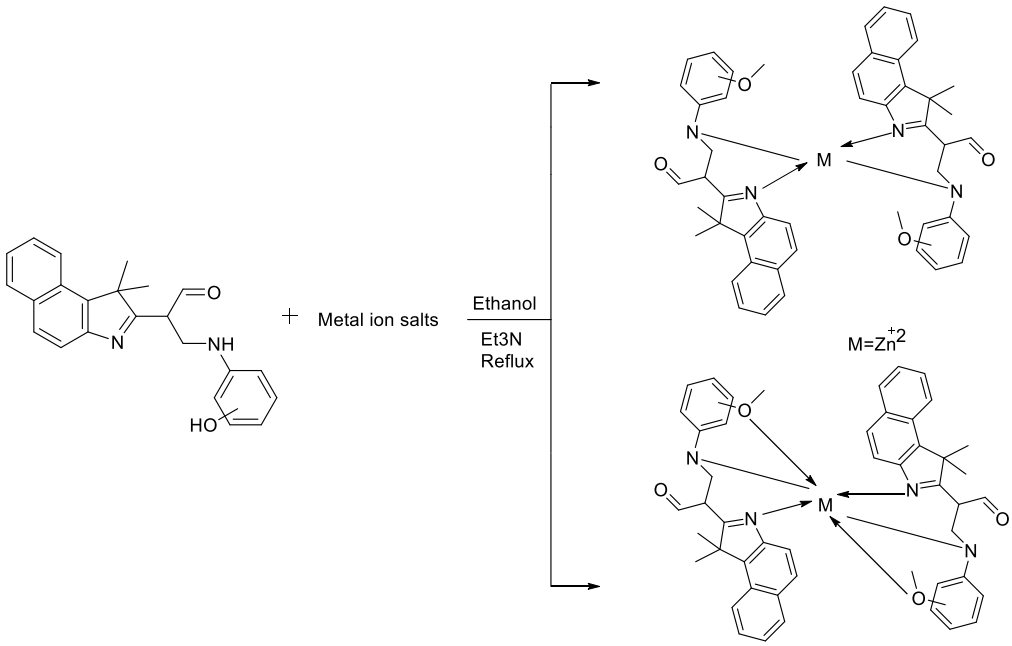


(2-10)

2- Synthesis of new derivatives by reacting isatin with different substituted aniline.



3- Synthesis a series of new complexes from the new synthesized compounds (2-10) with different transition metal ions and evaluation their biological activities.



4- Evaluating the anticancer activity for the synthesized compounds against other cell lines, and studying other biological activities of the synthesized compounds.

APPENDIXE

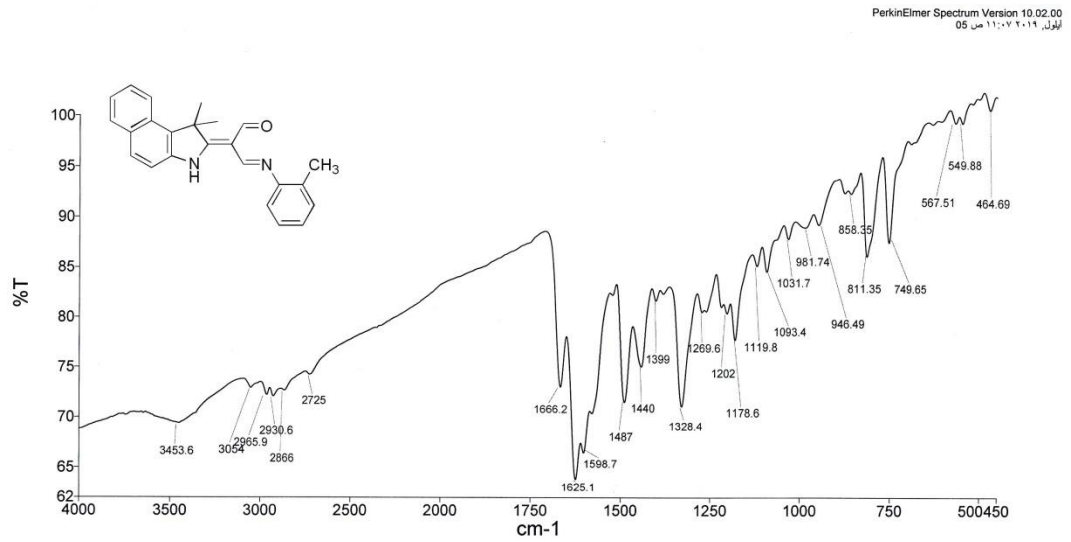


Figure (3. 16): The FTIR spectra of the compound (2)

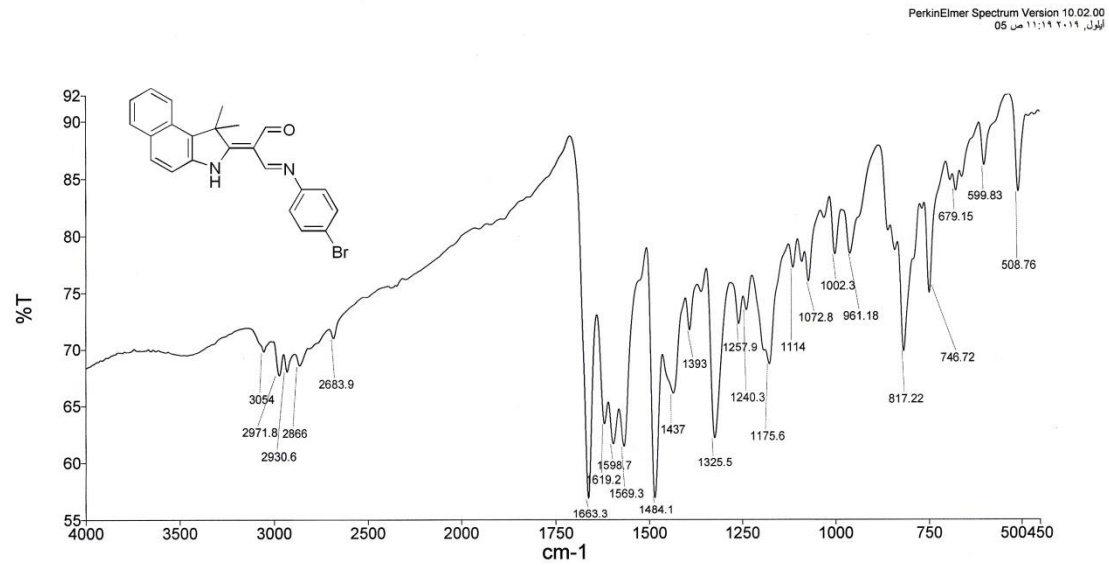


Figure (3. 17): The FTIR spectra of the compound (3)

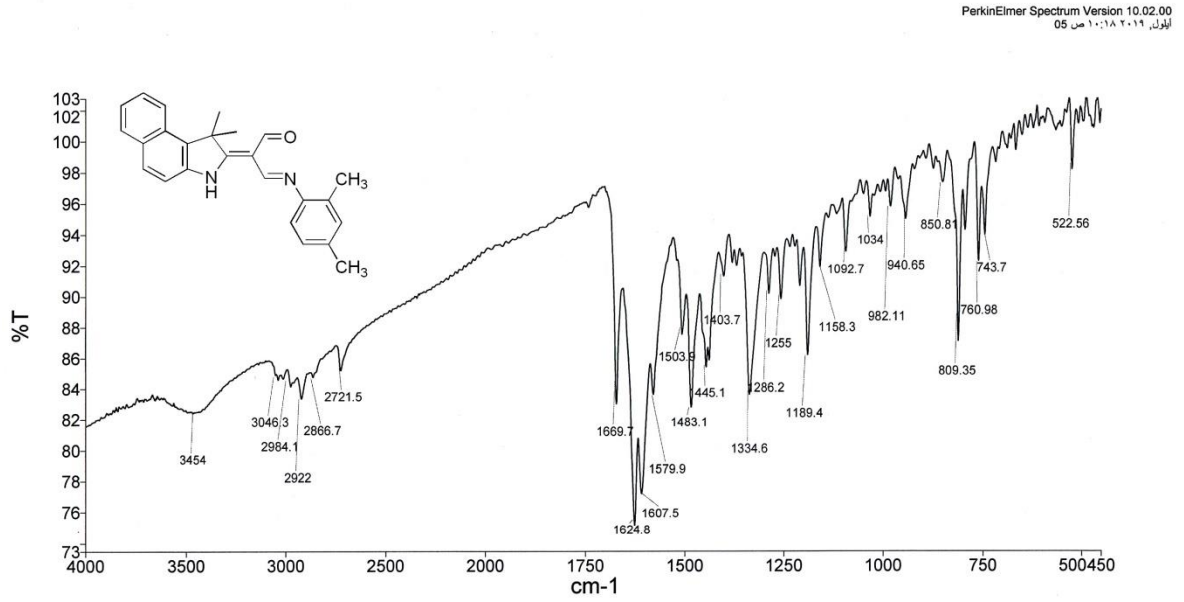


Figure (3. 18): The FTIR spectra of the compound (5)

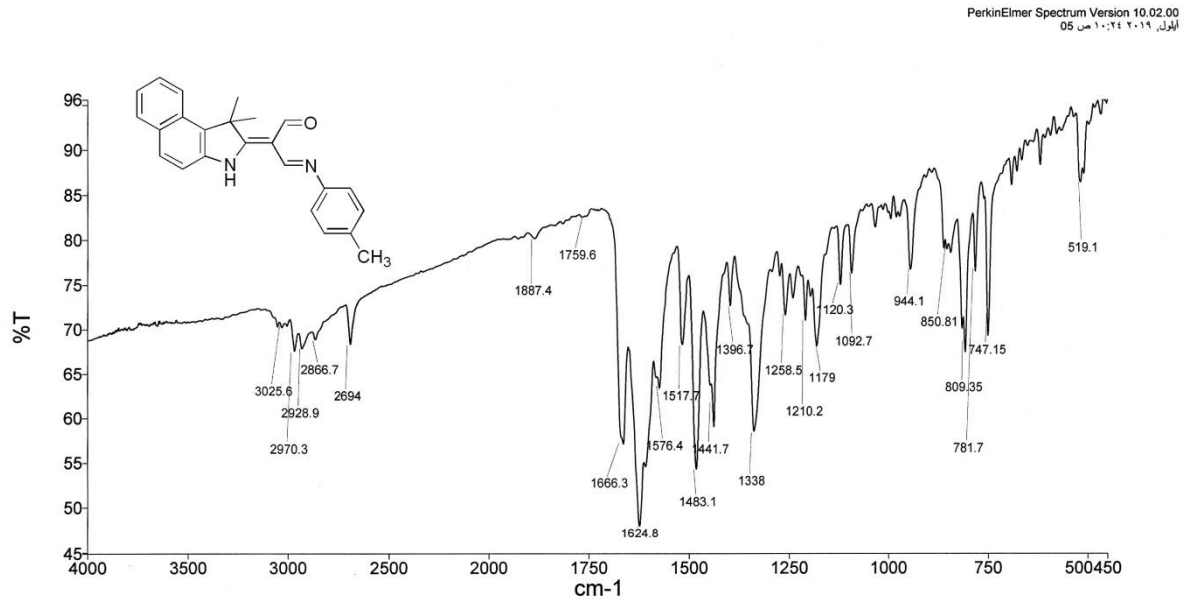


Figure (3. 19): The FTIR spectra of the compound (6)

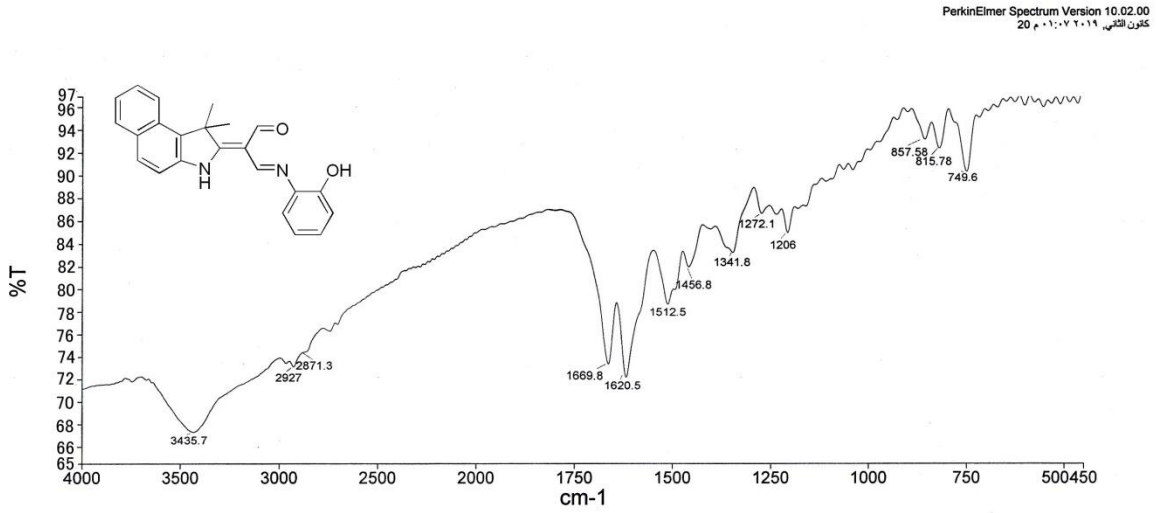


Figure (3. 20): The FTIR spectra of the compound (9)

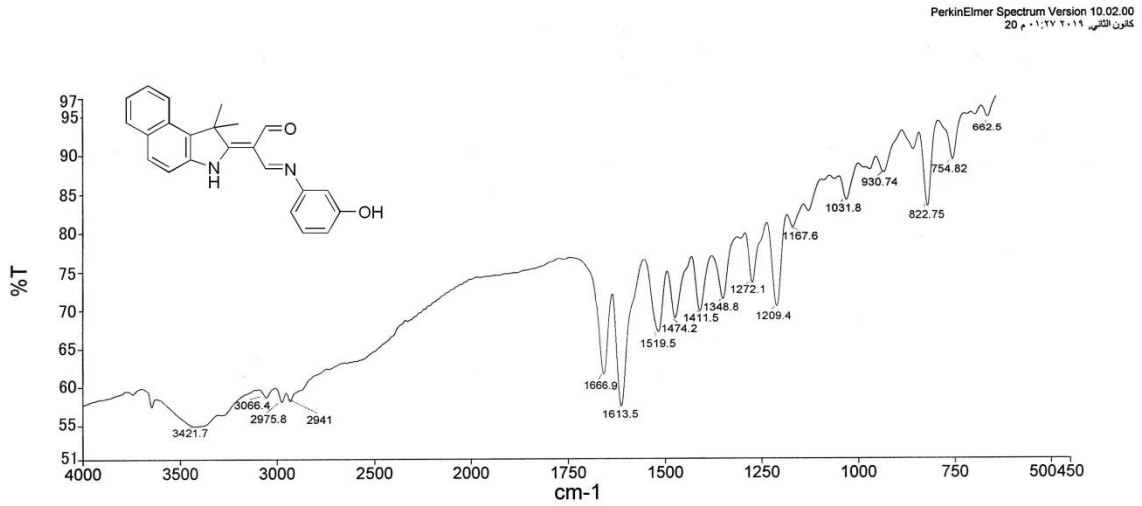


Figure (3. 21): The FTIR spectra of the compound (10)

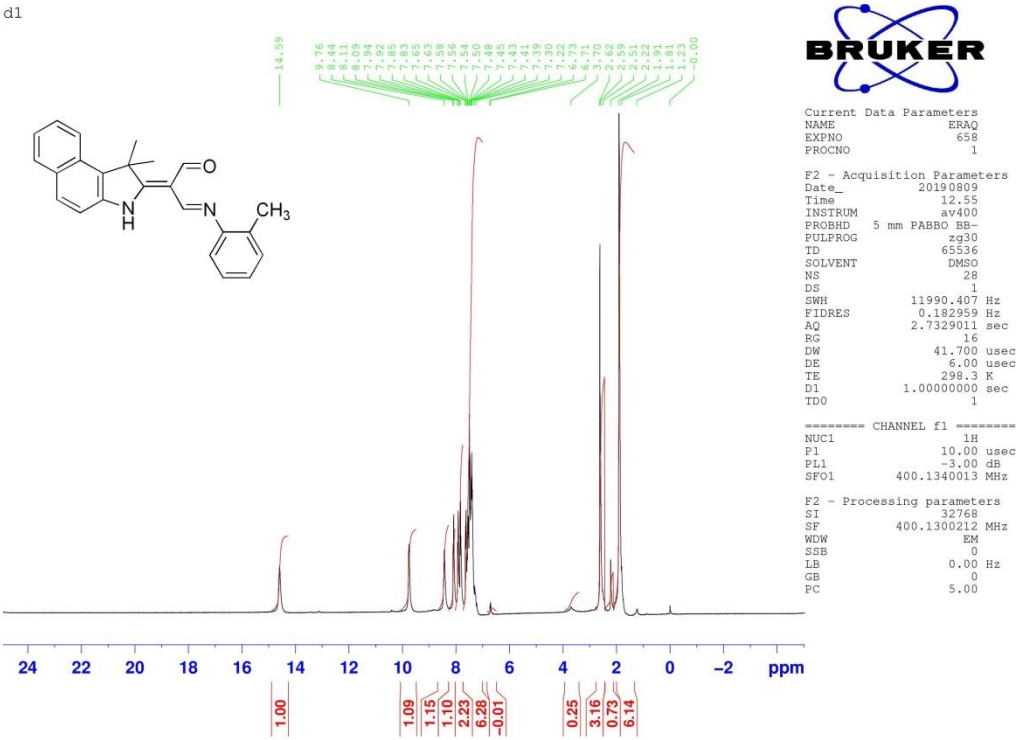


Figure (3. 22): ^{1}H-NMR spectrum of the compound (2)

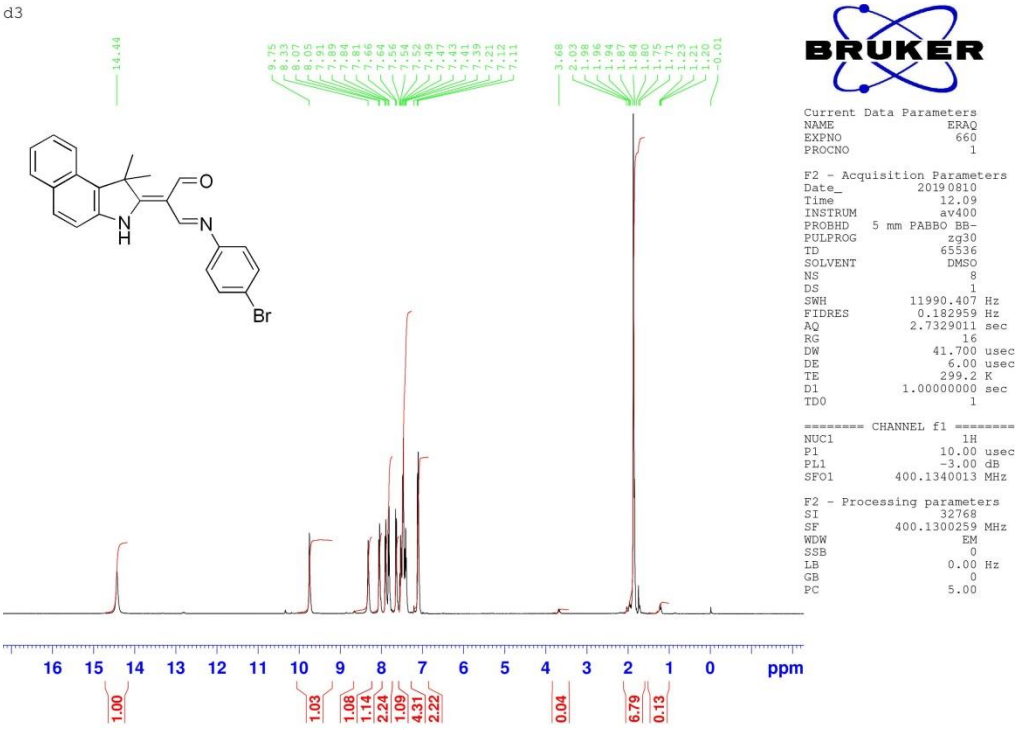


Figure (3. 23): ^{1}H-NMR spectrum of the compound (3)

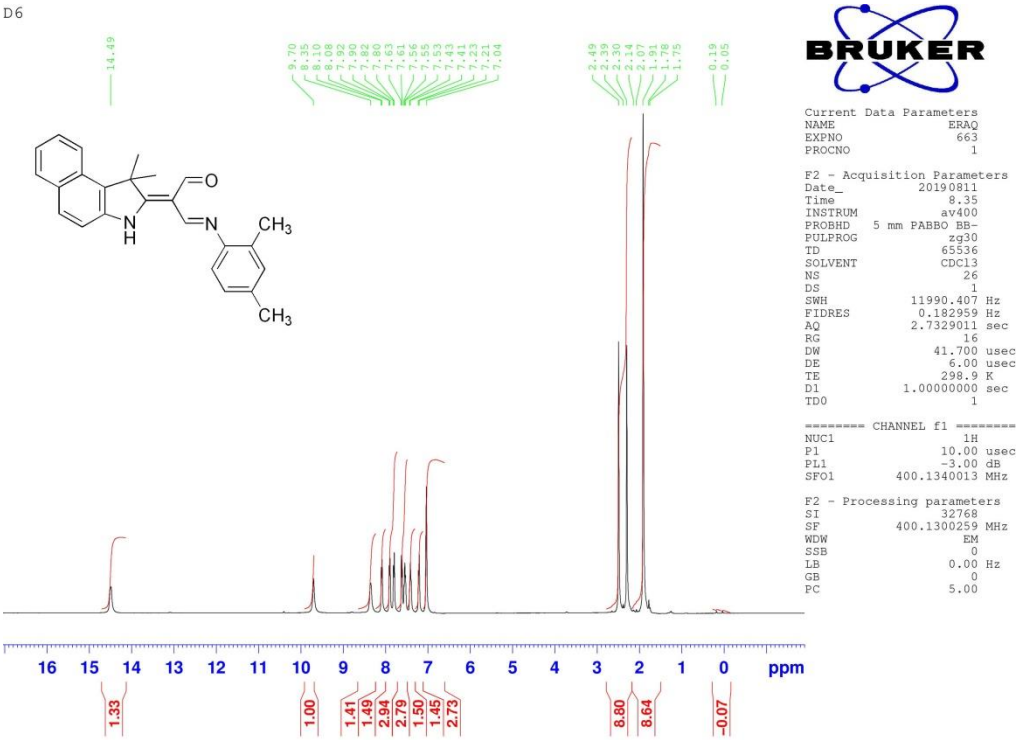


Figure (3. 24): ^{1}H-NMR spectrum of the compound (5)

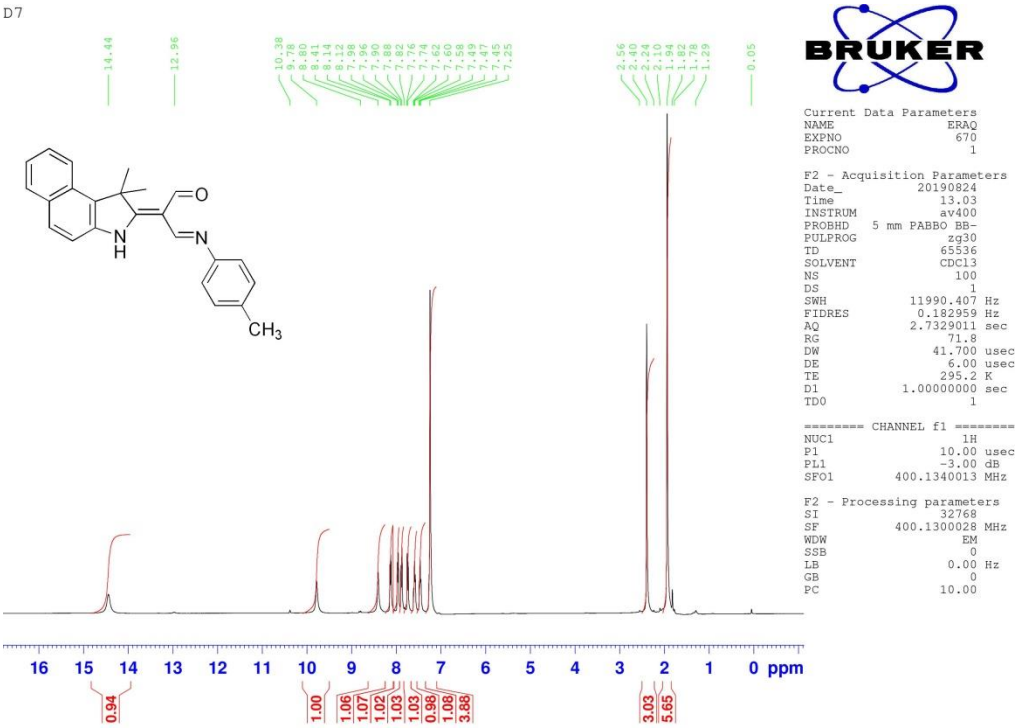


Figure (3. 25): ^{1}H-NMR spectrum of the compound (6)

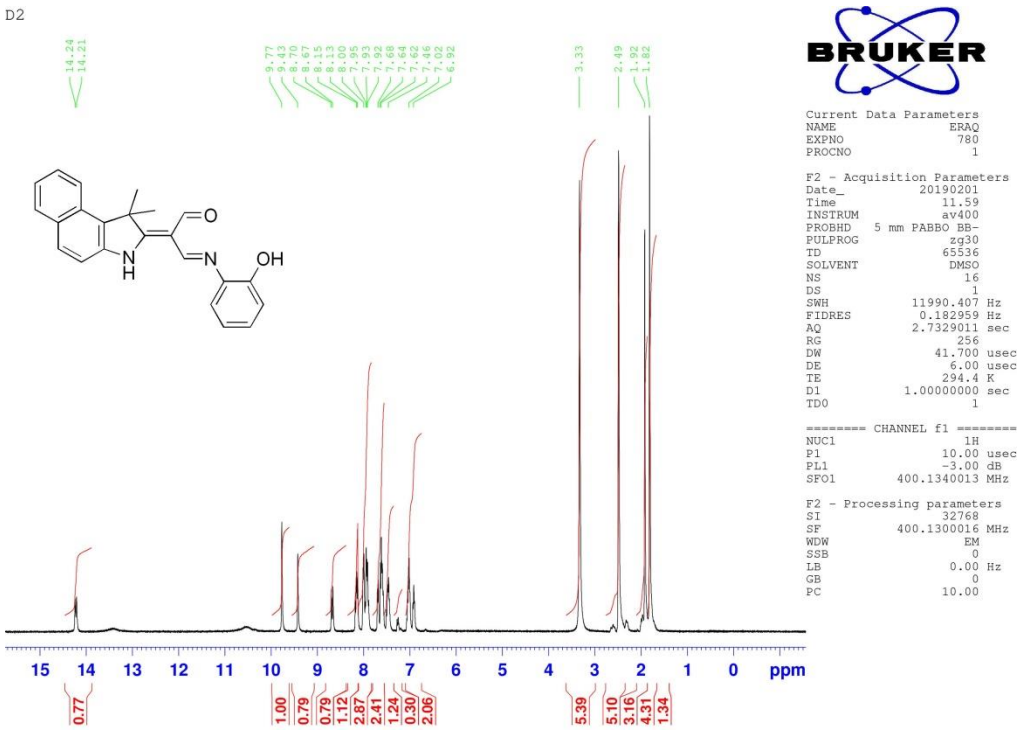


Figure (3. 26): ^{1}H-NMR spectrum of the compound (9)

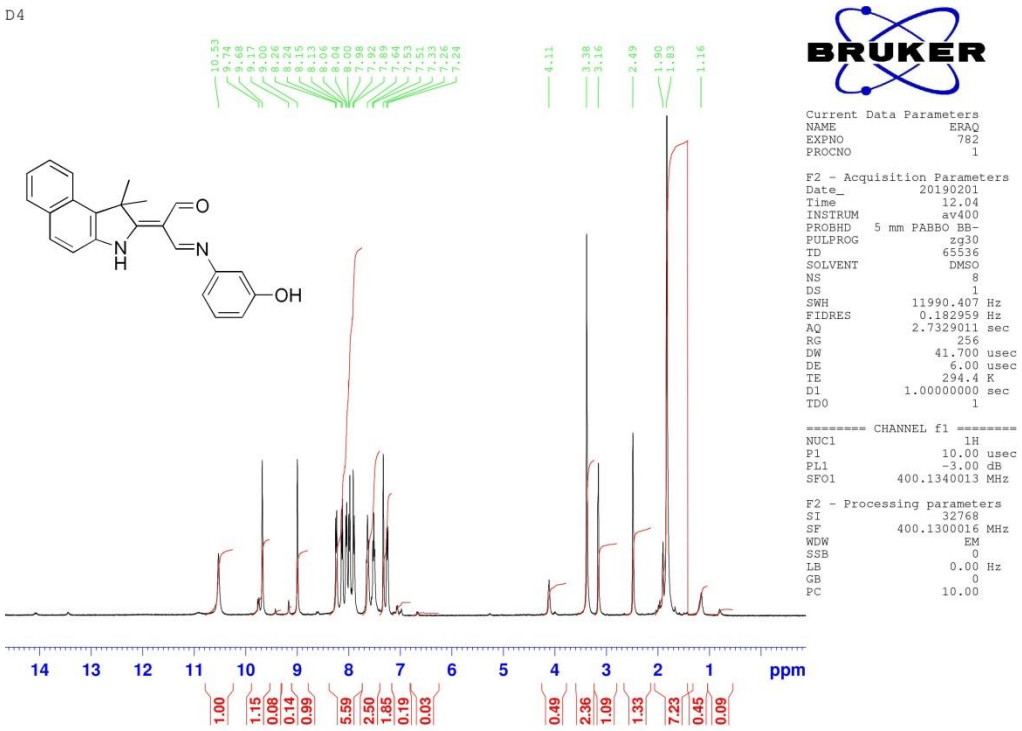


Figure (3. 27): ^{1}H-NMR spectrum of the compound (10)

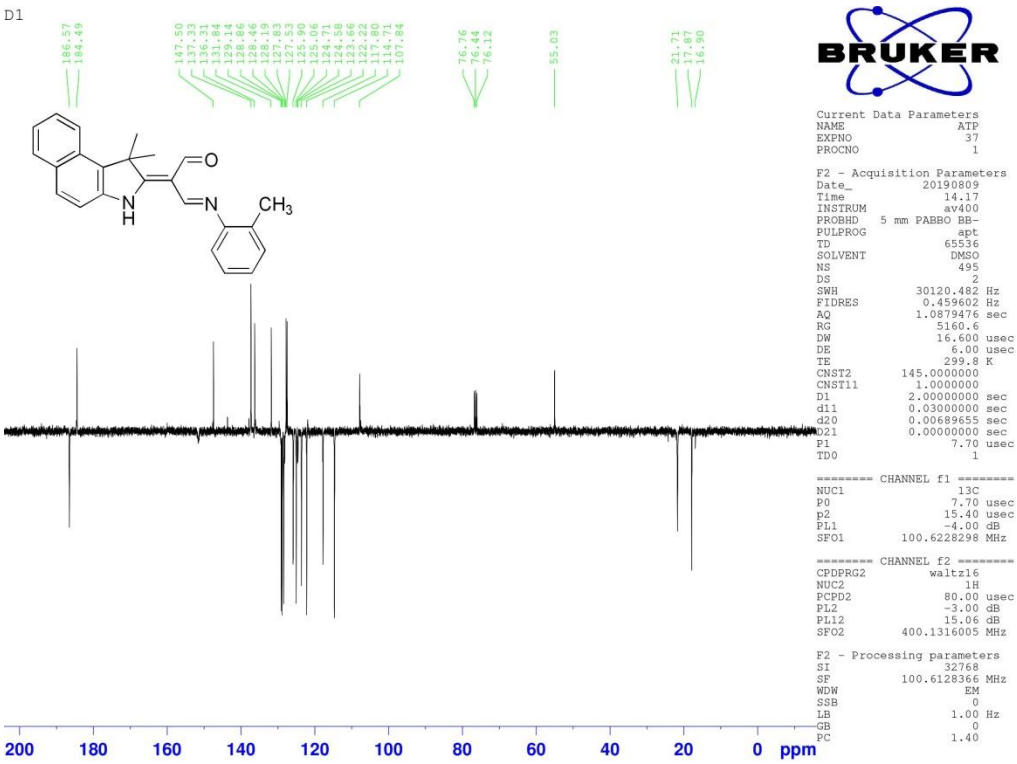


Figure (3. 28): APT ^{13}C NMR spectrum of the compound (2)

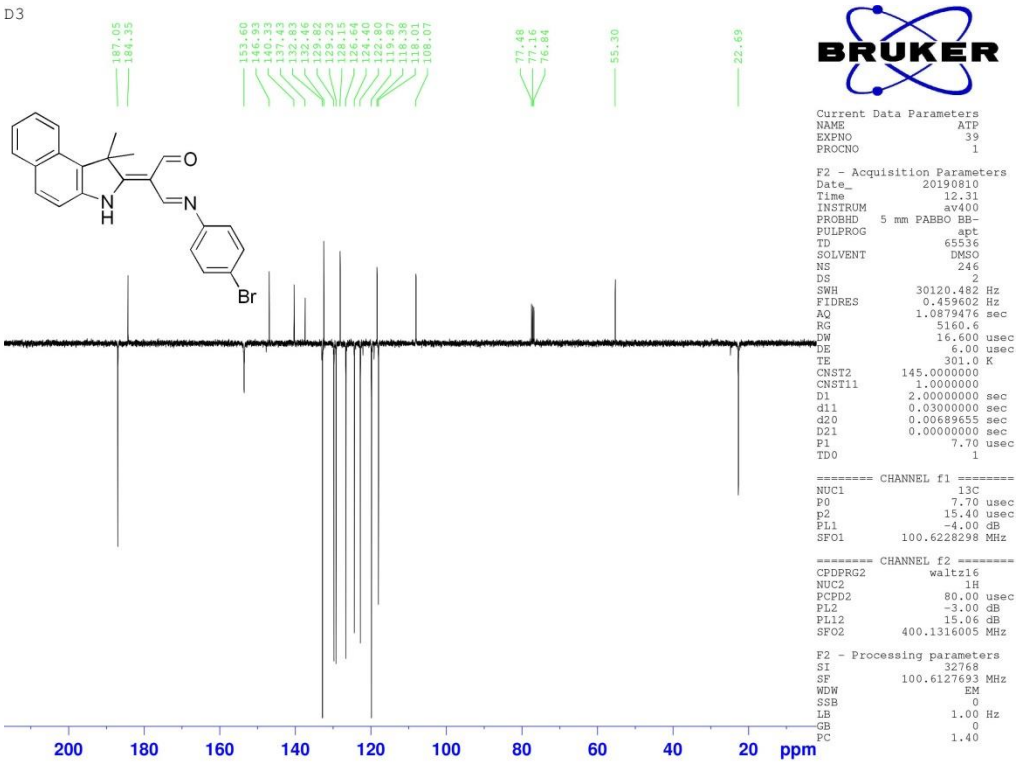


Figure (3. 29): APT ^{13}C NMR spectrum of the compound (3)

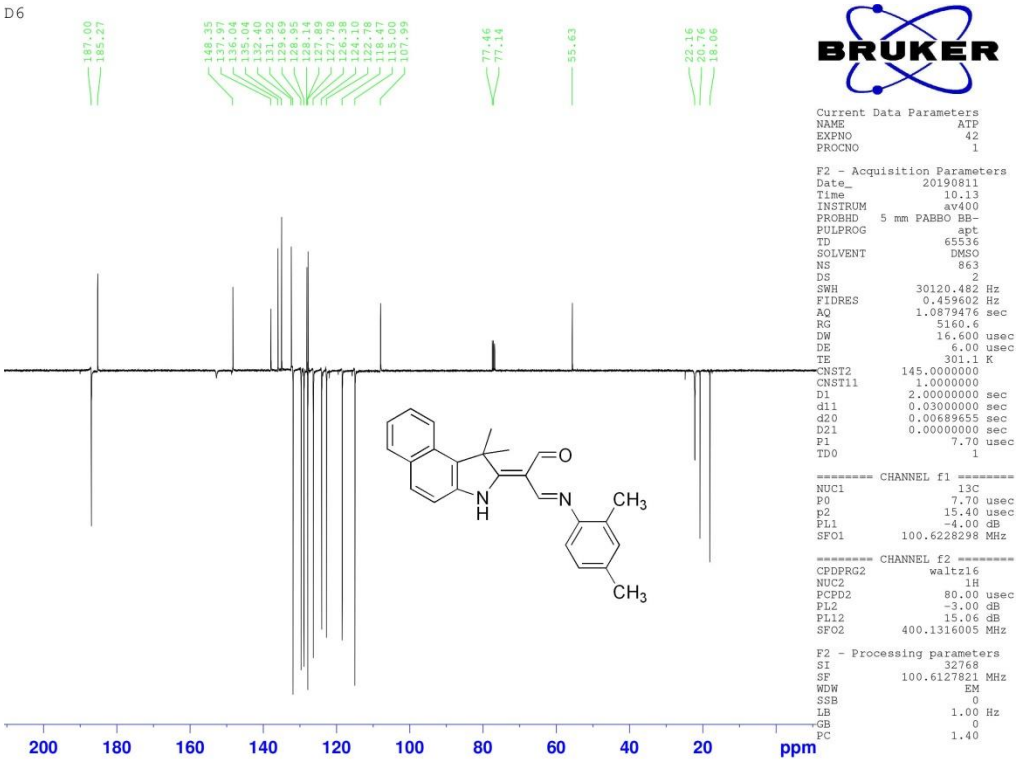


Figure (3. 30): APT ^{13}C NMR spectrum of the compound (5)

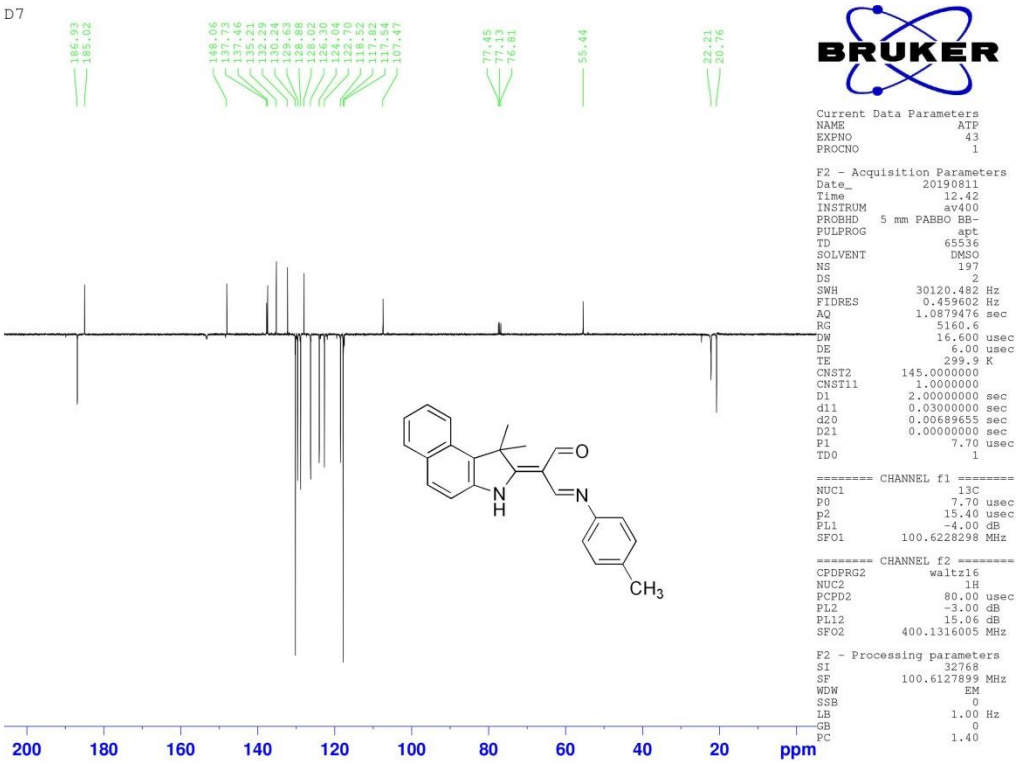


Figure (3. 31): APT ^{13}C NMR spectrum of the compound (6)

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REFERENCES

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الخلاصة

في هذه الدراسة تم تحضير مركبات جديدة لقواعد شيف من احد مشتقات الاندول وهذه المركبات هي :

١- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(o-propanal tolylimino)

٢- 3-((4-bromophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal

٣- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,3-dimethylphenyl)imino)propanal

٤- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2,4-dimethylphenyl)imino)propanal

٥- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(p-tolylimino)propanal

٦- 3-((4-chlorophenyl)imino)-2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal

٧- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-(phenylimino)propanal

٨- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((2-hydroxyphenyl)imino)propanal

٩- 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((3-hydroxyphenyl)imino)propanal

وتم تشخيصها واثبات تركيبها الكيمياوي بالتقنيات الطيفية مثل طيف الاشعة تحت الحمراء FTIR وطيف الرنين النووي المغناطيسي للبروتون والكاربون (^{1}H-NMR and ^{13}C-NMR APT) ونقاوتها اثبتت بواسطة كروماتوعرافيا الطبقة الرقيقة .معظم المركبات

المحضرة الجديدة تم دراسة تأثيرها البيولوجي ضد خلية AMJ-13 لسرطان الثدي واظهرت نتائج جيدة مقارنة مع الخلايا الطبيعية.

المركب (2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde) حضر بطريقة تفاعل فليسيمير-هاك من خلال تفاعل 1,1,2-trimethyl-1H-benzo[e]indole مع ثلاثي كلوريد الوفسفور ثنائي مثيل فورمايد كما موضح ادناه :

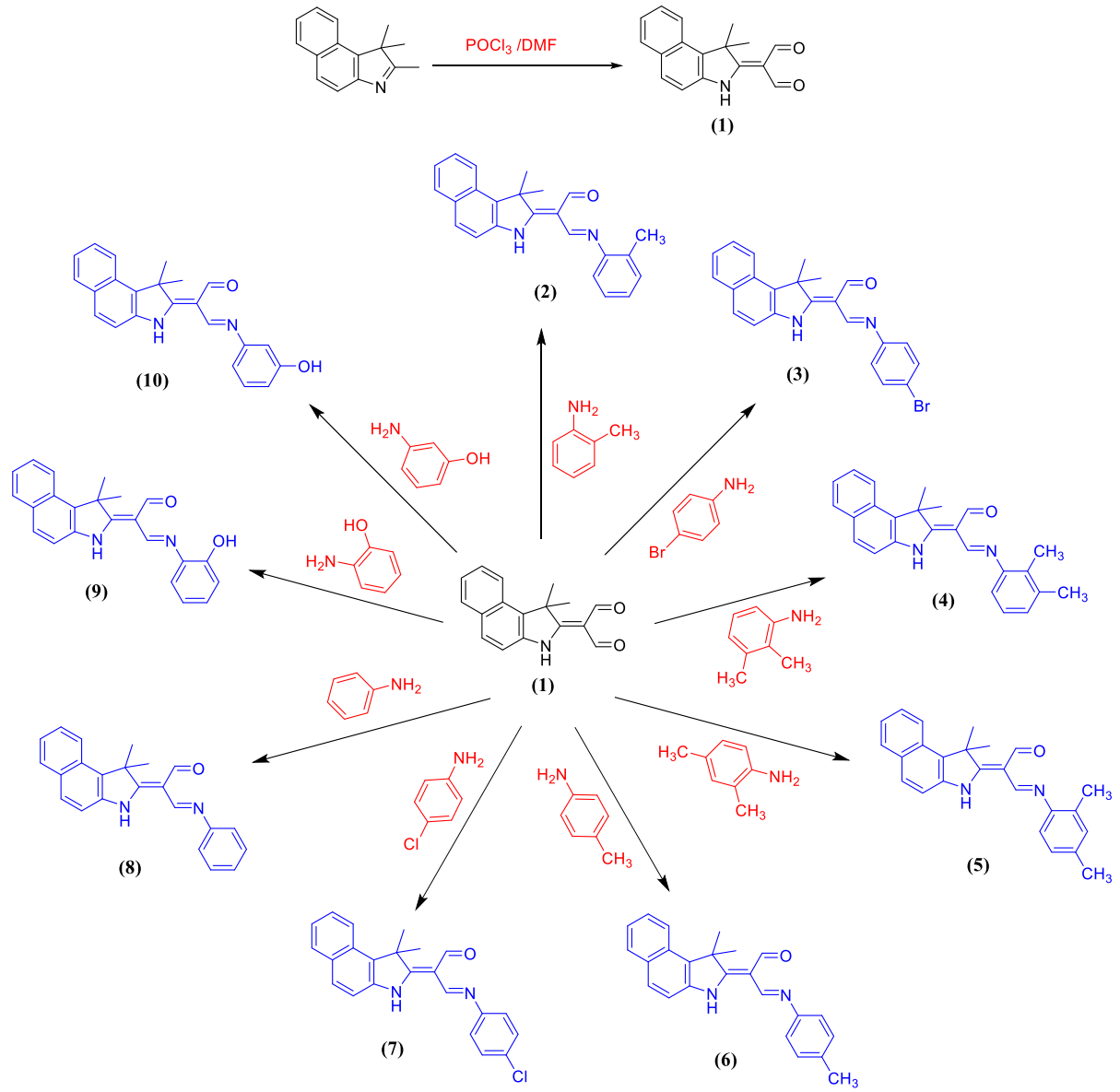
1,1,2-trimethyl-1*H*-benzo[*e*]indole

(1)

2-(1,1-dimethyl-1,3-dihydro-2*H*-benzo[*e*]indol-2-ylidene)malonaldehyde

المركب (١)هنا اعتبر كمادة بادئة لتحضير انواع مختلفة من الايمينات (قواعد شيف) من خلال التفاعل مع الانيلين وبعض من مشتقاتها كما مبين في الشكل ادناه.

تمت دراسة تأثير ستة من المشتقات المحضرة ضد خط الخلية AMJ-13 لسرطان الثدي باستخدام ثلاث تراكيز مختلفة (٢٥, ٥٠, ١٠٠) مايكروغم/مل خلال فترة تعريض ٤٨ ساعة. اظهرت هذه المركبات نسب تثبيط جيدة و واضحة ضد الخط المستخدم, من بينهم المركب (٨) اظهر اعلى نسبة من التثبيط ٦٧,٩ % عند اعلى تركيز ١٠٠مايكروغم /مل.



مخطط يوضح المركبات التي تم تحضيرها

وزارة التعليم العالي والبحث العلمي
جامعة ديالى/ كلية العلوم
قسم الكيمياء

تحضير وتشخيص مركبات عضوية جديدة مشتقة من 2(1,1-ثنائي مثيل-1,3- ثنائي هيدرو-H٢- بنزواندول-2-يليدين) مالونالديهايد وقياس فعاليتها الحيوية

رسالة مقدمة الى
مجلس كلية العلوم / جامعة ديالى
وهي جزء من متطلبات الحصول على شهادة الماجستير في علوم الكيمياء
من قبل الطالب

داليا عبد الستار جميل

بكالوريوس علوم الكيمياء / جامعة تكريت ٢٠١٥

بإشراف

أ.م. د. فاضل لفته فرج
٢٠٢٠ م

أ. م. د. وسن باقر علي
١٤٤١ هـ